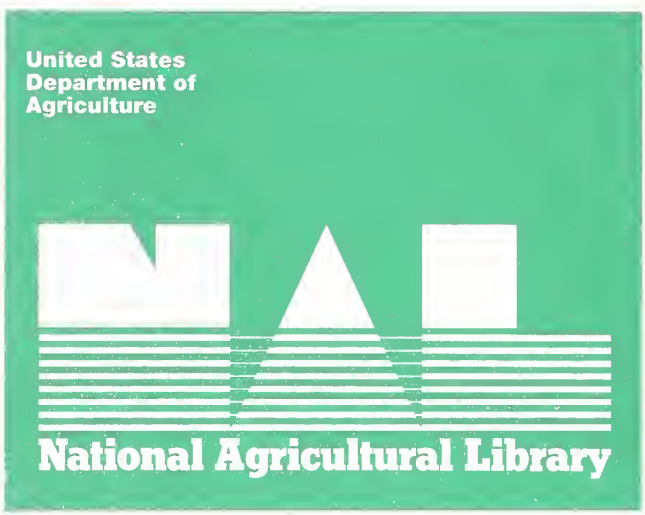
Gypsy Moth
Management
in the United States:
a cooperative approach

Draft
ENVIRONMENTAL IMPACT STATEMENT

Appendix F
Human Health Risk Assessment

1995

United States Department of Agriculture
Forest Service
Animal and Plant Health Inspection Service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Human Health Risk Assessment for the Gypsy Moth Control and Eradication Program

Final Draft

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Acronyms, Abbreviations, and Symbols

ai	active ingredient
AEL	adverse-effect level
ACGIH	American Conference of Governmental Industrial Hygienists
AChE	acetylcholinesterase
ATSDR	Agency for Toxic Substances and Disease Registry
B(a)P	benzo-a-pyrene
BCF	bioconcentration factor
BIU	billions of international units
B.t.k.	Bacillus thuringiensis var. kurstaki
bw	body weight
cfu	colony forming units
ChE	cholinesterase
cm	centimeter
2,4-D	dichlorophenoxyacetic acid
DDVP	2,2-dichloroethenyl dimethyl ester phosphoric acid (Dichlorvos)
DDT	dichlorodiphenyltrichloroethane
DFB	diflubenzuron
F	female
F_1	first filial generation
FSCBG	Forest Service Cramer Barry Grim Model
g	gram
GLEAMS	Groundwater Loading Effects of Agriculture Management Systems
HQ	hazard quotient
IARC	International Agency for Research on Cancer
kg	kilogram
$K_{o/c}$	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
Kp	permeability coefficient
L	liter
LC_{50}	lethal concentration, 50% kill
LD_{50}	lethal dose, 50% kill
LLE	loss of life expectancy
LOAEL	lowest-observed-adverse-effect level
m	meter
M	male

MCS	multiple chemical sensitivity
mg	milligram
mg/kg/day	milligrams of agent per kilogram of body weight per day
mm	millimeter
mm Hg	millimeters of mercury
mL	milliliter
mmol	millimole
MRL	minimal risk level
MW	molecular weight
NADH	nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
ng	nanogram
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NPV	nucleopolyhedrosis virus
NRC	National Research Council
OB	occlusion bodies
ppm	parts per million
PRZM	Pesticide Root Zone Model
PVC	polyvinyl chloride
RBC	red blood cells
RfC	reference concentration
RfD	reference dose
rpm	rotations per minute
RRV	risk reference value
SGPT	serum glutamate pyruvate transaminase
TLV	threshold limit value
TOTP	triorthotolyl phosphate
UF	uncertainty factor
μ	micron
μg	microgram
μm	micrometer
U.S.	United States
U.S. EPA	U.S. Environmental Protection Agency

$>$	greater than
$\geq$	greater than or equal to
$<$	less than
$\leq$	less than or equal to
$=$	equal to
%	percent
$\simeq$	approximately equal to

1. Introduction

This document addresses the potential human health effects associated with exposure to the gypsy moth and the agents used to control the gypsy moth, including formulations of Bacillus thuringiensis var. kurstaki (B.t.k.), Nucleopolyhedrosis virus (NPV), Diflubenzuron (DFB), DDVP, and Disparlure. As illustrated in Figure 1-1, the document is divided into nine sections: this introduction, the general methods used in the risk assessment, the health risks posed by the gypsy moth, the health risks posed by each control agent, and a comparative assessment of the risks associated with specific exposure scenarios for each agent. The risk assessment of each agent consists of:

a brief review of the properties and use of the chemical or biological agent,

an identification of the hazards associated with each agent,

an assessment of potential human exposure to the agent,

an assessment of the dose-response relationships for the agent,

and a characterization of the risks associated with exposure to the agent.

As discussed in section 2 regarding risk assessment methods, these basic steps follow the recommendations of the National Research Council of the National Academy of Sciences (NRC 1983) for the conduct and organization of risk assessments.

This risk assessment was used as a source of information during the preparation of the Environmental Consequences Chapter in the environmental impact statement for the gypsy moth and was prepared specifically for that purpose. Although this is a technical support document and addresses some highly specialized technical areas, every effort has been made to ensure that the document can be understood by individuals who do not have specialized training in the chemical and biological sciences. Certain technical concepts and terms common to all parts of the risk assessment are written in as plain a language as possible in section 2, risk assessment methods. In addition, they are defined in the glossary and in the list of acronyms, abbreviations, and symbols that accompany this risk assessment. Other more specialized terms and concepts are described as necessary when they appear in the text.

This document focuses on a concise characterization of human exposure to the gypsy moth and control agents and the toxicity of those agents. Thus, the risk assessments presented in this document are not, and are not intended to be, comprehensive in the sense that documents such as the toxicological profiles prepared by the Agency for Toxic Substances and Disease Registry (ATSDR) are comprehensive (ATSDR 1992). The purpose of this human health risk assessment is substantially different from the purpose of documents like the ATSDR

toxicological profiles. Toxicological profiles serve as generic and reasonably complete reference sources regarding the toxicity of a particular set of compounds. The toxicological profiles and similar documents are intended for use by individuals assessing a particular exposure scenario or set of exposure scenarios. The human health risk assessment is an assessment of such scenarios rather than the documentation for such an assessment and is intended for a much broader audience. Consequently, elaborate and largely academic discussions are avoided. Whenever available, recent and technically sound reviews are used to reference points that are not critical to a quantitative assessment. Although extraneous details are avoided, the document presents a discussion and description of key studies, defined as those directly applicable to the characterization of risk, in enough detail to permit the conclusions of the risk assessment to be evaluated without reference to the cited literature.

It is necessary to include detailed descriptions of some of the studies; therefore, the use of technical terminology in certain subsections of the document cannot be avoided. This point is particularly important in the subsections regarding hazard identification. To define each of the specific terms and, more importantly, to discuss their significance would increase the size of the document substantially and decrease its readability. As an alternative, each section of the document that contains highly technical material begins with a subsection called **Overview**. This section is written in plain language and presents all of the salient material contained in the remainder of the section.

Individuals who require only a summary of this risk assessment are referred to section 9, the comparative risk characterization. Section 9 summarizes the main conclusions of the risk assessment in plain language with a minimum of data summary. Individuals seeking a broader overview but wishing to avoid a detailed discussion of the available data may wish to read the program description (subsection 1) and the risk characterization (subsection 5) of each of the major sections on the individual agents. All of these sections are written in plain language.

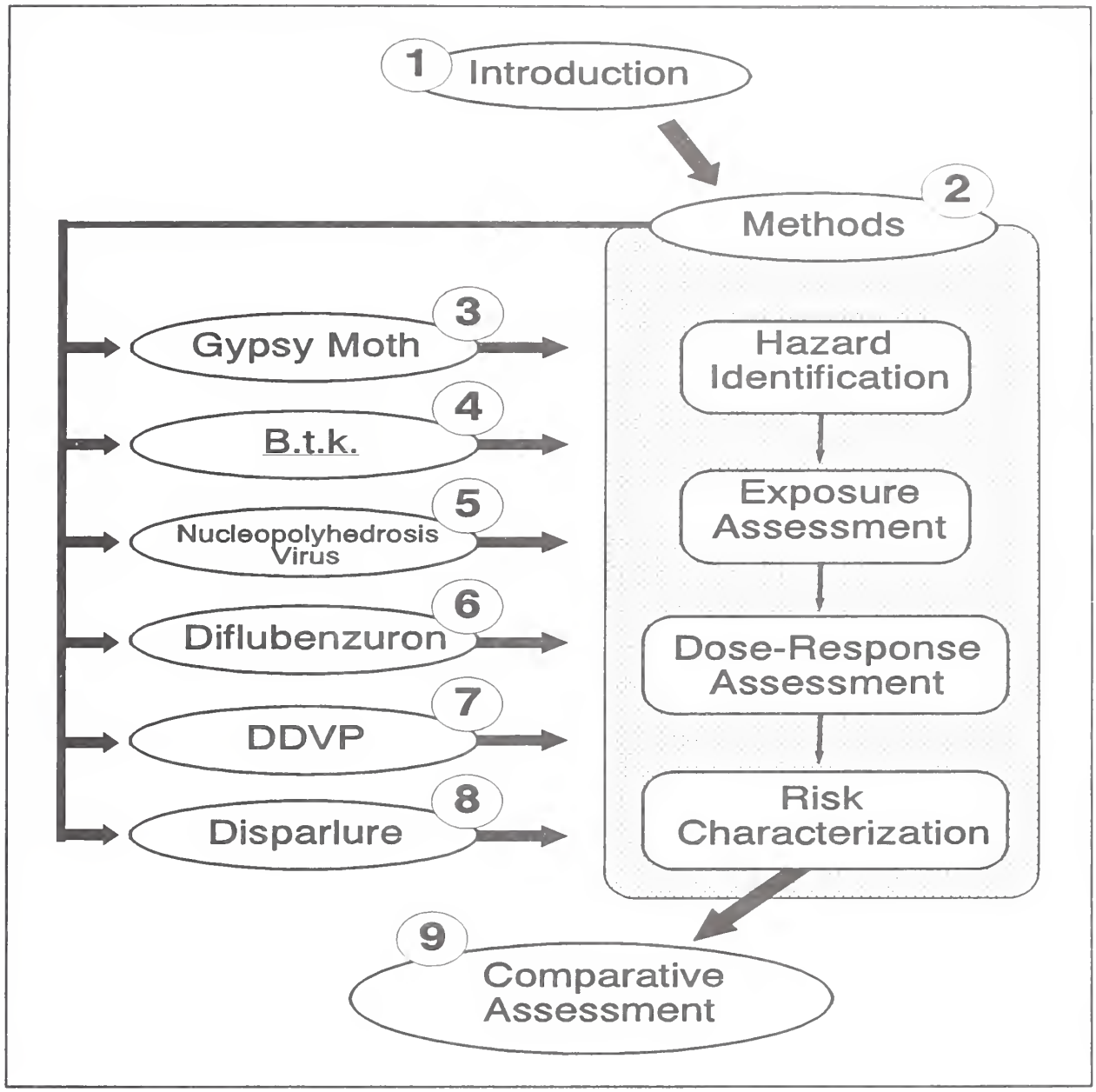


Figure 1-1. Overview of the Human Health Risk Assessment. This figure illustrates the organization of the document. The document is divided into nine sections (section numbers shown in circles): the introduction, the general methods used in the risk assessment, the health risks posed by the gypsy moth, the health risks posed by each control agent, and a comparative assessment of the risks. For each agent, the risk assessment consists of a hazard identification, exposure assessment, dose-response assessment, and risk characterization.

2. Risk Assessment Methods

2.1. Overview

This section describes the methods used in the risk assessment of each of the agents under review. The procedures are similar to those recommended by the National Research Council of the National Academy of Sciences (NRC 1983). As illustrated in Figure 2-1, risk assessments are conducted in four stages: hazard identification, exposure assessment, dose-response assessment, and risk characterization. Hazard identification is the process of determining whether a particular agent can be associated with one or more adverse effects. If one or more effects can be identified, two parallel processes are initiated: exposure assessment and dose-response assessment. The exposure assessment defines plausible exposure scenarios and attempts to estimate levels of exposure in each scenario. For chemical and biological agents, these levels of exposure are usually converted to an exposure dose, in units of mg agent/kg body weight/day, which is usually abbreviated as mg/kg/day. The dose-response assessment relates levels of exposure to adverse effects and, possibly, the likelihood of observing these effects. Sometimes, a quantitative exposure assessment or dose-response assessment cannot be conducted because of limitations in the available data, in which case, a quantitative risk assessment cannot be made. If a quantitative exposure assessment and a quantitative dose-response assessment can be conducted, they are used to develop one or more quantitative risk characterizations. Otherwise, the risk can only be characterized qualitatively. Each risk characterization attempts to answer two questions: Given the results of the exposure assessment, what effects might be observed and how serious are the effects? If a quantitative characterization is possible, it will attempt to answer the additional question: What is the likelihood that the effects will be observed? If the available data do not justify making quantitative assessments, it may be possible, nonetheless, to express, qualitatively, the likelihood of observing adverse effects.

As illustrated in Figure 2-1, risk assessments are not conducted in a vacuum. Although risk assessment is intended to be the objective application of the aforementioned four-stage process, risk assessments are initiated in response to a perceived risk and are intended to support risk management. Risk management interprets the risk assessment in the context of additional factors, including the feasibility of control, economics, and public concern. Risk management results in the selection of alternatives to be pursued in a given situation. In addition to taking actions--or in some cases taking no action--risk management involves the communication of risk. Depending on the circumstances, this communication will be directed either to public officials who must make certain decisions that affect risk or to the general public who are subject to or otherwise affected by a potential risk. Whether it is the result of a risk assessment or of some other factor in the risk management process, risk communication is intended to affect risk perception by clearly explaining the nature of a perceived risk or placing the risk in a broader perspective.

2.2. The Nature of Risk

Although risk may be defined simply, it is usually complex to express and interpret. A reasonable definition is (Klaassen and Doull 1975 p. 12):

> Risk is the probability that a substance will produce harm under specified conditions.

General discussions about risk and the problems associated with expressing it are presented in a number of publications (for example, Brown 1989, Greenland and Robins 1994, Susser 1993). The discussion of risk presented here is basic to the understanding of how risks associated with the gypsy moth and gypsy moth control measures can be expressed and put into perspective with one another and with other types of risk.

As illustrated in Table 2-1, some risks are expressed as a probability. For instance, 900 people in the United States were killed by falling objects in 1988 (Cohen 1991). Assuming that all individuals are at risk of being hit by a falling object and using 250 million as the approximate population of the United States in 1988, the annual risk of being killed by a falling object can be calculated as $3.6 \cdot 10^{-6}$

$$900 \text{ people} \div 250 \text{ million people} = 3.6 \cdot 10^{-6}.$$

Throughout this document, probability and other numerical values are expressed using **scientific notation**. For example, $3.6 \cdot 10^{-6}$ indicates that the first number (3.6) is multiplied by 10 to the specified power (-6). By definition, $1 \cdot 10^{-6}$ is equal to 0.000001 or 1 in 1 million. Thus, $3.6 \cdot 10^{-6}$ is equal to 0.0000036. Numbers that differ from one another by several orders of magnitude (powers of 10) are usually easier to compare when using scientific notation (see back cover). In the text, calculations are often shown on a separate line. For example,

$$900 \text{ people} \div 250 \text{ million people} = 3.6 \cdot 10^{-6}.$$

Some simple two component calculations are included in parentheses within the text.

Although the calculation regarding the risk of being struck by a falling object may be a useful gross measure of risk, most risks are conditional and may be related to a number of factors. For example, 10,600 deaths were attributed to occupational accidents in 1988. Using the above approach, the risk for the U.S. population could be calculated as $4.2 \cdot 10^{-5}$

$$10{,}600 \div 250 \text{ million} = 4.2 \cdot 10^{-5}.$$

Although this could be taken as a gross measure of risk, it is misleading. By definition, only workers are subject to this risk. Thus, a better expression of this risk can be calculated by dividing the incidence of mortality in workers by the total number of individuals who worked

during 1988. The resulting risk estimate for workers would increase. The risk of being killed on the job for individuals who do not work would be zero. Thus, a gross measure of risk can be converted to conditional risk (that is, the risk of one event, such as death, given that another event, such as working, occurs). For workers, still better estimates would account for the number of days worked, assuming that the more an individual works the greater the risk. Other improvements could involve an expression of risk that accounts for the type of job and characteristics of the workers such as age, sex, salary, or general health status. These additional risk factors, if not accounted for in a study, can lead to erroneous conclusions. Thus, they are often referred to as **confounders** in discussions of studies on human populations.

The distinction between conditional and unconditional risk is critical in general and for this risk assessment. For example, as discussed in section 7 on DDVP, an individual who tampers with and grossly mishandles a plastic strip containing DDVP is likely to experience some type of adverse effect. The conditional risk is high. Based on the available data, however, the probability of the condition (that is, tampering and gross mishandling) appears to be quite low.

Other dimensions of risk include the nature of the affected population and the duration of the effect. For example, Cohen (1991 p. 317) asserts that "... the premature death of an elderly person is less regrettable than the death of a young person" and derives an expression of risk based on loss of life expectancy (LLE). This method involves expressing risk as the sum of age-specific risks and age-specific life expectancies. Although this approach may raise ethical questions, it is conceptually similar to the approach that considers the duration of the effect as a measure of severity. For an effect of fixed biological severity, most people would agree that the longer the effect lasts the more adverse it is. In the case of calculating the LLE, which applies only to mortality, the duration and, hence, the adversity of the effect is measured as a loss of life expectancy, the only meaningful measure of duration for this effect.

Regardless of the method of expressing risk or the severity of risk, the issue of the acceptability of the risk must be considered. Although components of this question are clearly beyond the scope of a risk assessment, insight into the question can be obtained by examining common risks, several of which are summarized in Table 2-1 and illustrated in Figure 2-2.

In Figure 2-2, common risks are plotted with two types of axes, linear and logarithmic. Linear axes are common and intuitive. Equal distances on a linear axis represent equal differences in values. Thus, the distance between 10 and 20 is the same as the distance between 110 and 120. Logarithmic axes are somewhat less intuitive but can be very useful for illustrating differences in numbers that encompass a wide range of values. Equal intervals on a logarithmic or log scale represent equal ratios. Thus, the difference between 10 and 100, a factor of 10, is the same as the difference between 100 and 1,000, another factor of 10.

Table 2-1 is adapted from Cohen (1991) and expresses the risk of dying from various causes, based on statistics from 1988. For the sake of comparison, risks are given as probabilities and LLE in days. Two types of probabilities are given, risks per year and lifetime risks. Risks per year can be somewhat misleading, as in the case of worker risk discussed above. Lifetime risks, on the other hand, adjust for differences in the duration over which an individual is at risk. Thus, to calculate the average lifetime risk associated with working, the annual risk for 1988 is multiplied by 45, assuming that an individual will work for 45 years. Because the probability of specific risks may vary over time, these calculations serve only as rough approximations.

Two basic types of risks are summarized in Table 2-1, voluntary and involuntary. There is a substantial difference in how individuals regard risk, depending upon whether or not the risk is voluntary. In general, individuals are willing to accept a much higher risk if the risk is voluntary (Weisensel 1989). This is apparent from the data summarized in Table 2-1. Some individuals accept voluntary risks such as parachuting, mountain climbing, hang gliding, and scuba diving, which are greater than the risk of death from all accidents combined. Most individuals do not avoid activities such as swimming and various forms of transportation associated with lifetime involuntary risks in the range of $1 \cdot 10^{-5}$ to $1 \cdot 10^{-2}$. Without condoning or endorsing any specific risk level, U.S. EPA assessments often present doses associated with cancer risks of $1 \cdot 10^{-6}$ to $1 \cdot 10^{-5}$ (U.S. EPA 1987a, 1989a). Within the perspective of the data given in Table 2-1, these might be regarded as levels of involuntary risk generally accepted by the public.

The acceptability of risk is also related to perceived benefit. Activities like parachuting, mountain climbing, hang gliding, and scuba diving, which are clearly hazardous, may be accepted by some individuals because of recreational or psychological value. The acceptance of other risks may be supported by an explicit comparison of risks. For example, one estimate of the annual risk of death from jogging is about $1.3 \cdot 10^{-4}$, which corresponds to an LLE of 1.7 days per year of jogging or 50 days for a lifetime, assuming that the individual jogs for 30 years (Cohen 1991). Jogging is usually considered beneficial in maintaining cardiovascular fitness. Based on the analysis presented by Cohen (1991), heart disease is associated with an LLE of 2,100 days. Consequently, if jogging reduces the probability of developing heart disease by more than 2.4%

$$50 \text{ days} \div 2{,}100 \text{ days} = 0.024,$$

the risk of jogging is acceptable in that jogging will lower the overall risk to the individual (that is, it will increase the life expectancy of the individual). The issues of acceptable and comparative risk are directly germane to this risk assessment because health risks are associated both with controlling and failing to control the gypsy moth. These issues are discussed in sections 3 through 8 and compared in section 9.

In the discussion above, risk is expressed simply as a probability. Some adverse effects, however, are more serious than others. This risk assessment uses a simple scheme to

characterize severity in making dose-response assessments (section 2.5). The issue of severity is important to this risk assessment because most of the effects likely to occur after exposure to the gypsy moth or after exposure to agents used to control the gypsy moth are relatively mild. More severe effects are far less likely to occur. Thus, both probability and severity must be considered when comparing these different risks.

2.3. Hazard Identification

Hazard identification is the process of identifying the array of potential effects that an agent may induce in an exposed human population. This process involves gathering all relevant information and assessing this information to determine which effects the agent is likely to induce for each potential route of exposure. Hazard identification is the first and most critical step in any risk assessment. Unless some plausible biological effect can be identified, a risk assessment cannot be completed.

In the hazard identification, a review of the most relevant data on health effects is presented. The analysis involves making judgments about which effects can be attributed to the agent under review and which effects are relevant to the assessment of human health. Although hazard identification is a qualitative process, quantitative methods are used to assess causality in dose-response or dose-severity relationships. Of these two relationships, the dose-severity relationship is generally more relevant for noncarcinogenic effects. The severity scale used to conduct this risk assessment uses four levels of severity (Table 2-2). This scale, with minor differences in nomenclature, is used by many government agencies to classify the toxicological effects observed in experimental or epidemiology studies.

All of the commercial formulations used to control the gypsy moth contain adjuvants or additives, which are considered inert ingredients. **Inert** in this context means that the compounds do not cause mortality in the gypsy moth. These inerts may be toxic to humans, however, and are considered in the hazard identification as well as the subsequent stages of the risk assessment. Two general approaches, mixture-based and component-based, can be used for assessing inerts. The mixture-based approach uses toxicity information on the commercial formulation, which includes the inerts. Using the terminology of the U.S.EPA (1986a) guidelines for the risk assessment of complex mixtures, this approach is based on the **mixture of concern**. The second approach involves examining the individual components in each formulation. This approach is facilitated by using the U.S. EPA (1989b) classification of inert ingredients, which places each of approximately 1,200 inerts on one of four lists. Lists 1 and 2 consist of approximately 50 chemicals each that are of high concern either because of known toxicity (List 1) or suspected toxicity (List 2). List 4 contains approximately 300 chemicals that are generally recognized as safe. List 3 has approximately 800 chemicals for which there is insufficient information to classify the agents.

The hazard identification also includes the identification of biologically sensitive subpopulations. The term **biologically sensitive** refers to a group of individuals who,

because of their developmental stage or some other biological condition, are more susceptible than the general population to a chemical or biological agent in the environment. Individuals at greater risk because of increased exposure are addressed in the exposure assessment (section 2.4). Biologically sensitive subpopulations do not include individuals who are at the extreme lower end of a simple (unimodal) distribution of tolerances. The distinction between sensitive individuals in a normal population and a biologically sensitive subgroup is illustrated in Figures 2-3 and 2-4.

Figure 2-3 illustrates the standard normal distribution. The term **standard normal distribution** is used here in the formal statistical sense described in any basic text on statistics (for example, Mendenhall 1975). In terms of toxic response, the distribution can be interpreted as a description of individual tolerances or threshold doses. If an individual is subjected to a dose above the individual's threshold, the individual will respond; otherwise, the individual will not respond. These individual thresholds will vary among members of a population, and the way in which this variation occurs is referred to as a distribution. Many different types of distributions have been described statistically, one of which is the standard normal. The standard normal distribution, by definition, has a mean of zero and a standard deviation of one. The mean of zero indicates that the average tolerance in the population is zero. In terms of dose, the assumption is often made that the distribution of tolerances has a log normal distribution (Finney 1971).

In any normal distribution, one standard deviation encompasses about 34% of the population. Thus, as illustrated in Figure 2-3, 0 ± 1 standard deviation encompasses about 68% of a population. The area between 1 and 2 standard deviations, encompasses about 13.6% of the population. Because the normal distribution is symmetrical, by definition, 13.6% of the population is also encompassed by the area between -1 and -2 standard deviations. The further the deviation from the mean, the less likely is the tolerance. As illustrated in Figure 2-3, only about 2.2% of the population will have tolerances between -3 and -2 deviations from the mean, and only about 2.5% of a population will have tolerances that are less than the tolerance at two standard deviations below the mean. These individuals might be referred to as sensitive in that their tolerance is less than that of about 97.5% of all other individuals in the population. Other definitions of sensitivity, based on different percentages, may be used arbitrarily. This kind of variability does not suggest that these individuals are qualitatively different from other individuals in the population. The biological factors that govern response are assumed to vary, and these individuals are simply at the lower extreme of this variation.

In contrast, Figure 2-4 illustrates a sensitive subpopulation. In this figure, a plot of the individual thresholds, labeled exposures, versus the frequency of these thresholds clearly indicates a bimodal or two-spiked population distribution. The large bell-shaped curve to the right can be regarded as the normal population, analogous to that in Figure 2-3. The smaller bell-shaped curve to the left indicates the biologically sensitive subgroup. This bimodal distribution pattern indicates that a group of individuals is in some way biologically different

because their extreme sensitivity cannot be described by a **normal** distribution in the statistical sense.

A failure to differentiate clearly between biologically sensitive subpopulations and sensitive individuals in a unimodal population can cause substantial confusion in a risk assessment. Conceptually, the welfare of sensitive individuals in a simple distribution is incorporated into the dose-response assessment by the use of uncertainty factors (section 2.5). There is less assurance that such standard uncertainty factors will account for the susceptibility of biologically sensitive subgroups. An emerging body of evidence indicates that there are subpopulations that are intrinsically more sensitive than the general public to certain agents in the environment (NRC 1993a). Nonetheless, the risk assessment community has not reached a consensus regarding the prevalence of these conditions of extreme sensitivity or a method for the quantitative incorporation of this information into a risk assessment. The hazard identification focuses on information about the possible existence of sensitive subpopulations. This information is incorporated into the risk characterization, as discussed in section 2.5.

Concern with sensitive subgroups is enhanced by the emerging issue of multiple chemical sensitivity (MCS). MCS is a poorly understood syndrome (NRC 1993a). Individuals believed to have MCS are extremely sensitive to chemicals at extremely low levels of exposure. Although many of the symptoms are similar to those of allergies, individuals with MCS claim sensitivity to a very broad range of chemicals. Although reports of this condition have been cited in the literature for many years, the lack of specificity and the variability of the symptoms led some researchers to doubt that this is a single disease (Miller 1994). Although some clinicians have suggested that MCS may be more psychosomatic than physiological, mechanisms involving time-dependent sensitization have been proposed that would account for the spectrum of responses demonstrated by individuals with this condition (Bell 1994a). Although this is still a matter of debate in the literature, at least some government agencies recognize MCS as a disability (Weidenfeller 1992).

2.4. Exposure Assessment

Exposure assessment is the process of estimating the extent to which a population will come into contact with an agent. Exposure assessments involve three general steps: characterization of the exposure scenario, estimation of levels in environmental media (such as air, food, or water), and calculation of dose rates.

Exposure scenarios describe the ways in which individuals may be exposed to a particular agent. The exposure scenarios considered in this risk assessment are determined by the application method and the physical and toxicological properties of the agent. Depending on the properties and application method, the risk assessment of each agent considers acute, subchronic, or chronic durations of oral, dermal, inhalation, or combined exposure to the insecticide by the general population and by workers mixing, loading, or applying the insecticide.

Three general types of exposure scenarios are considered: routine, extreme, and accidental. Routine exposures assume that the recommended application rates are used and that recommended safety precautions are followed. Furthermore, routine exposures are based on the most likely estimates of modeling parameters such as food or water consumption rates and values for skin surface area exposure. Extreme exposures assume that recommended procedures and precautions are not followed and use more conservative, but still plausible, values for model parameters that increase the estimate of exposure. Moreover, extreme exposures consider only acute durations because it is not plausible to assume that safety recommendations will be completely disregarded or that individuals will consume extraordinary quantities of contaminated media for prolonged periods. Accidental exposures assume some form of equipment failure or gross human error. Although these are worst case scenarios within the context of the risk assessment, they are designed, nonetheless, to represent realistic, not catastrophic, events. Some accidental exposure modifiers are specific to a program activity; others are simple extensions of extreme exposure scenarios. Like extreme exposure scenarios, accidental exposure scenarios consider only acute exposure. Not all exposure assessments involve all three types of scenarios. For some scenarios (the direct ingestion of materials in a trap, for example), only one scenario (accidental) is appropriate. The decision about whether or not to use a particular scenario is based on the applicability of the scenario to the particular agent and the need to encompass uncertainties in the potential exposures.

Additional variability is considered by estimating exposed or absorbed doses for individuals of different age groups (that is, adults, young children, toddlers, and infants). Children may behave in ways that increase their exposure to insecticides: long periods of outdoor play or the consumption of contaminated media or materials, for example (NRC 1993b). In addition, there is not a linear relationship between anatomical and physiological factors (body surface area, breathing rates, and consumption rates for food and water) and body weight and age (U.S. EPA 1988a, 1989c). Consequently, the models used to estimate the exposure dose (mg/kg body weight/day) based on chemical concentrations in environmental media (ppm in air, water, or food) generally indicate that children, compared with adults, are exposed to higher doses of chemicals.

After characterizing the necessary exposure scenarios, various exposure assessment methods are applied to estimating levels of the agent in environmental media, such as air, soil, and water. The specific methods used depend on the quality of the available monitoring data, the extent to which relevant and validated environmental fate models are available, and the complexity of the exposure scenario.

For complex scenarios, such as aerial application, both environmental fate models and monitoring data may be used. For aerial applications, for instance, the Forest Service Cramer Barry Grim (FSCBG) model can be used to predict aircraft spray dispersion and deposition above and within vegetation canopies (Teske and Curbishley 1990). Groundwater models such as the Groundwater Loading Effects of Agriculture Management Systems (GLEAMS) (Davis and others 1990) or the Pesticide Root Zone Model (PRZM) (U.S. EPA

1984) can be used to estimate transport in soil and soil water. These environmental fate models are useful because environmental conditions and application rates within the model can be varied to reflect the routine, extreme, and accidental scenario modifiers. Nonetheless, these models have estimation errors that can be difficult to characterize. Consequently, monitoring data are used directly in the exposure assessment, whenever possible, and may be supplemented by exposure models, as necessary.

In some simple exposure scenarios, correspondingly simple models or calculations are used. For example, the concentration of insecticide in a small contained pond can be estimated directly as a function of the application rate and depth of mixing. This estimate can be used to support the exposure scenarios such as a toddler drinking directly from a backyard pond shortly after application of the insecticide.

If the consumed quantity of a toxic agent is known (as in the accidental ingestion of a known quantity of insecticide), this quantity is simply divided by body weight to convert the intake amount to a dose. When material containing a known or estimated concentration of toxic agent is consumed, the intake may be expressed as the product of the concentration and the quantity of contaminated material consumed. Reference values, such as human body weights and consumption rates, are taken from standard sources (U.S. EPA 1988a, 1989c). For the most part, the use of these reference values is straight forward, as detailed in the appropriate section on each agent. For children, however, the use of these values in oral and dermal assessments is potentially confusing. For oral exposures, reference values for the consumption of contaminated media such as water are provided for a 10 kg child. For dermal exposures, reference values for skin surface area are provided for an 11 kg child but not a 10 kg child. Thus, in the risk assessments for some agents such as Diflubenzuron, a 10 kg child is used for oral exposures and an 11 kg child is used for dermal exposures.

2.5. Dose-Response Assessment

The dose-response assessment describes the degree or severity of risk as a function of dose. Two general types of dose-response assessments are conducted in this risk assessment. For noncarcinogenic effects, most dose-response assessments involve the use of a NOAEL-uncertainty factor approach. For carcinogenic effects, a dose-response model is used to estimate cancer risk. Other dose-response models are used occasionally to assess risks associated with noncarcinogenic effects.

2.5.1. NOAEL-Uncertainty Factor Approach

The NOAEL-uncertainty factor approach used in this risk assessment is similar to that used by U.S. EPA (1987) and ATSDR (1992). The risk reference value (RRV) is an estimate of dose that is not likely to induce adverse health effects in humans. This is similar to many other types of toxicological assessments (Table 2-3). To derive an RRV, an experimental

dose (NOEL, NOAEL, or AEL) associated with the most sensitive effect is identified. By definition, the most sensitive effect is the adverse effect observed at the lowest dose level. This dose is divided by the product of a series of uncertainty factors intended to account for differences between experimental exposure and the conditions for which the RRV is being derived. The basic equation is:

$$RRV = \frac{EL}{\prod_{i=1}^{n} UF_i} \qquad (1)$$

where:

EL = *NOEL, NOAEL, or LOAEL* (*Table* 2-2)

UF_i = *the* i^{th} *uncertainty factor*

n = *number of uncertainty factors* (*Table* 2-4)

The uncertainty factors used in this risk assessment and in risk assessments made by other government agencies are presented in Table 2-4. Each of the uncertainty factors has some level of experimental support and each is intended to be conservative (Dourson and Stara 1983). The use of multiple uncertainty factors involves a multiplication of conservative assumptions. This conservativism in the derivation of RRVs is grounded in the history of risk assessment (Dourson and Stara 1983). From its inception, the focus of risk assessment has been the development of criteria--levels of exposure that are defined in some way as safe. Consequently, the methods used in regulatory toxicology are intentionally conservative. This conservative design, conceptually similar to redundant safety systems in aircraft, is appropriate for systems that may affect public health and have general and widespread use.

Figure 2-5 illustrates the process of deriving an RRV. Hypothetical dose-severity data are plotted for two effects, designated by circles and squares. Assume that both effects are of equal concern and that the studies on both effects are of equal quality. For both effects, three data points are available for each severity category. The effect designated by circles is the most sensitive effect because it has the lowest AEL (LOAEL). In this example, the LOAEL can be associated with a NOAEL, labelled **Basis for the RRV** in Figure 2-5. In other cases, a NOEL or NOAEL for the most sensitive effect may not be available, so a LOAEL may be used directly. As summarized in Table 2-4, this increases the size of the uncertainty factor. Once the appropriate NOEL, NOAEL or LOAEL is identified, the uncertainty factors are applied to estimate the RRV.

Depending on the nature of the experimental NOAEL or LOAEL and the RRV being derived, the relationship of the experimental data to the RRV may be remote. The most extreme case, the use of a subchronic LOAEL to estimate a chronic RRV, is illustrated in Figure 2-6. In this figure, area is used to represent dose. The outer square represents the experimental measurement, a subchronic LOAEL. Each successively smaller square represents the application of one of the uncertainty factors of 10. The smallest square,

barely discernable in the center of this figure, is the RRV. The ratio of the experimental measurement to the RRV in this example is 10,000. On the other extreme, directly relevant toxicological data may be available. For instance, data are available on the effects of a B.t.k. formulation on workers (section 4.4). As illustrated with the B.t.k. example and discussed in section 4.5, substantial uncertainties may still remain in the risk assessment because of limitations in the exposure assessment or aspects of the hazard identification.

2.5.2. Dose-Response Models

Dose-response assessments for cancer use the linearized multistage model and the general procedures outlined by U.S. EPA (1987a). The multistage model has the form:

$$P = 1 - e^{-\left(\sum_{i=0}^{n} q_i \cdot d^i\right)} \qquad (2)$$

where:

P = *probability of response*
n = *the number of stages used in the model*
q_i = *the* i^{th} *slope factor*
d = *dose*
e = *a constant equal to approximately* 2.3

The principal reason for selecting the U.S. EPA model is to defer to the recommendation by the National Research Council of the National Academy of Sciences (NRC 1983) that federal agencies adopt the same risk assessment methods when possible. Although a discussion of the relative merits of a simpler model verses the linearized multistage model is beyond the scope of this discussion, this approach adds a minimum of complexity and has the benefit of several desirable properties, including considerations of nonlinear dose-response patterns and the sample sizes in the experiment (Crump and Howe 1984).

For noncarcinogenic effects, other dose-response models used in this risk assessment include the simple linear model and the probit model. The general form of the linear model, as detailed in most basic texts on statistics, is:

$$Y = mx + b \qquad (3)$$

The model includes two variables: Y is the variable being estimated, also referred to as dependent variable, and x is the explanatory or independent variable. The model also has two parameters: m is the slope of the linear equation and b is the intercept. In toxicology and risk assessment, the most common notation for the model is:

$$P = md + b \quad (4)$$

where P is the probability or some other measure of response and d is a measure of dose or exposure.

The probit model (Finney 1971) is a form of the linear model based on the normal distribution, described in the hazard identification (section 2.3). In this model, the proportion of responders is converted to units of probits, which are essentially measures of the standard deviation from the mean or 50% response level. By convention, a response of 50% is assigned a probit of 5.

As illustrated in Figure 2-3, the area under the curve between 0 and one standard deviation below the mean is 0.34 or 34%. Thus, the area under the standard normal curve up to one standard deviation below the mean is 0.16

$$1 - (0.5+0.34) = 0.16.$$

Consequently, a probit of 4 corresponds to a response rate of 16%. Most often, the X-axis is expressed in units of log dose or some other measure of exposure. The transformation of proportions to probits and dose to log dose is intended to linearize the dose-response relationship. In other words, a plot of probit-response against log dose approximates a straight line. The most common notation for this model is:

$$Y = \alpha + \beta\log(d) \quad (5)$$

where β is the slope, α is the intercept, and Y is the response in probits.

The selection of a particular mathematical model may be governed by biological principles, as in the use of the multistage model (U.S. EPA 1987a). In other cases, the use of the model may be based on the observation that the model fits the experimental data. This, in general, is the justification for the probit model: the log-dose probit-response transformation has been shown to fit the dose-response data for many different chemical and biological agents (Finney 1971).

Two general measures of model fit are the squared correlation coefficient, often referred to as r^2, and the p-value for the slope. The r^2 is a measure of the proportion of the variability in the data accounted for by the model: the higher the number, the better the model fits the data. The p-value is the probability that the slope is zero. If the slope is zero, the independent or explanatory variable used in the model does not explain the behavior of the dependent variable. The lower the p-value the more significant is the association. Usually, a p-value of less than 0.05 is associated with statistical significance, although the selection of this value is arbitrary.

Both statistical significance and model fit are related to another statistical measure, referred to as **degrees of freedom**. This is simply the number of data points minus the number of parameters in the model. For instance, two points are needed to define a straight line. In statistical jargon, using two points to define a straight line is fitting a two-parameter model with zero degrees of freedom. In this case, no estimates of model fit or correlation are possible because all of the information (that is, the data points) is used to estimate the parameters; hence, no information is left to assess the quality of the fit. The use of data models with limited degrees of freedom is a practical concern for the dose-response assessments of the gypsy moth (section 3.4) and B.t.k. (section 4.4).

Two factors must be appreciated in selecting a model. First, within the observable range, most reasonably flexible models give satisfactory fits to most reasonable data sets. This is illustrated in Table 2-5 and Figure 2-7 for four data points fit to three two-parameter models. The simple linear model best fits the available data. Nonetheless, the other two-parameter models, the multiplicative and exponential model, also fit the data well--the r^2 is greater than 0.9 and the p-values are less than 0.05--even though the shapes of these models differ substantially from one another and from the shape of the linear model. Furthermore, within the range over which observations are available, the estimates of response differ by less than a factor of 2. In the low dose region, however, the multiplicative model, compared with the other two models, gives risks that are much lower.

The differences in the agreement between the various models in the high and low dose regions illustrate the difference between interpolation and extrapolation. Interpolation is the use of mathematical models within the range of observations. In Figure 2-7, this region ranges from 1 to 40 mg/kg/day. Extrapolation is the use of a mathematical model to make estimates outside of the observable range. With the exception of carcinogenic risks, this risk assessment uses models primarily to interpolate risks. Thus, model selection is not generally a major source of uncertainty. Exceptions to this statement are discussed, as necessary, in the dose-response assessments of the individual agents.

The second factor in the use of mathematical models concerns the measure of risk. In Figure 2-7, both the linear and exponential model lead to measures of risk at a dose of zero. This is often referred to as the background response. In expressing risks associated with exposure to an agent, these background responses are factored out of the dose-response assessment by using only the slope parameter from the model. Using the linear model in Table 2-5 as an example and assuming that dose is expressed in units of mg/kg/day, the slope for the linear model is 0.011 $(mg/kg/day)^{-1}$. This indicates that for each mg/kg/day, risk increases by 0.011. Thus, at a dose of 25 mg/kg/day, the estimate of extra risk is approximately 28%

$$25 \text{ mg/kg/day} \cdot 0.011 \text{ (mg/kg/day)}^{-1} = 0.275.$$

In this risk assessment, **extra risk** is defined as the risk in the population that can be attributed to exposure to the agent.

In some instances, experimental data directly related to the exposure of concern are not available; consequently, various adjustments on dose are necessary. This occurs most commonly with carcinogenic effects. As described above, the risk assessment uses cancer slope factors for carcinogenic effects. A major limitation in the use of these factors is that many exposure scenarios involve brief periods of time, compared with the human life span. Most studies that serve as the basis for cancer potency factors, however, are conducted over periods of time that approximate the lifetime of the animal. For short-term exposures, the U.S. EPA guidelines for carcinogenic risk assessment (U.S. EPA 1987a) recommend that the effect of a short-term exposure on lifetime risk be calculated as:

$$R = \frac{SL_{(mg/kg/day)^{-1}} \cdot d \cdot Duration\ of\ exposure}{Life\ span} \quad (6)$$

where **SL** is the slope for cancer risk based on a lifetime exposure scenario, **d** is the daily dose, and the duration of exposure as well as life span are measured in the same units.

The use of the equation 6 is an example of a general relationship in toxicology referred to as Haber's law (Amdur 1980):

$$Exposure \cdot Time = Constant \quad (7)$$

This relationship is true for some chemicals and some endpoints but not true for others. Even when true for a particular chemical and effect, it may be true only over certain ranges of exposure. Relatively small adjustments are more plausible than large adjustments. Using Haber's law for carcinogens often involves dividing an exposure period of 1 day by the reference human life span of 70 years or 25,550 days, in which case, the resulting risk estimate is highly uncertain (U.S. EPA 1991a, 1991b). Although this method is used in this document, it is recognized that risk may be over or under estimated and the level of uncertainty cannot be well characterized. Such adjustments and their attendant uncertainties are discussed, as necessary, in the individual dose-response assessments of each agent.

2.6. Risk Characterization

Risk characterization is the process of comparing the exposure assessment with the dose-response assessment to express the level of concern regarding an exposure scenario or set of scenarios (NRC 1983). This document conducts risk characterizations accordingly and generally implements the risk characterization process detailed by U.S. EPA (1989a). Because some of the exposures discussed in this risk assessment may occur over prolonged periods, the cumulative effects of such exposures are described in each risk characterization. In addition, some individuals may be exposed to more than one control agent and all individuals will be exposed to additional chemical and biological agents during control activities. Considerations of such exposures or connected activities are also explicitly addressed in each risk characterization.

2.6.1. Hazard Quotients and RRVs

By definition, an RRV is intended to represent an exposure that is not expected to cause adverse effects in humans. Consequently, if an estimated or anticipated exposure is below the RRV, this exposure scenario would not be considered hazardous. This obvious consequence has been formalized by EPA (1989a) into the hazard quotient (HQ), which is used for the risk characterization of noncarcinogenic effects. The method for calculating the HQ is:

$$HQ_{rd} = \frac{E_{rd}}{RRV_{Rd}} \qquad (8)$$

where:

HQ_{rd} = *route and duration specific hazard quotient*

E_{rd} = *exposure by the specified route and duration*

RRV_{rd} = *RRV for the specific route and duration*

Units for exposure and the RRV will be route dependent. Usually, for oral exposure, the units will be expressed in mg/kg/day. For inhalation exposure, the units will be expressed in mg/m^3. For dermal exposure, there may be two RRVs: one expressed in units of mg/kg/day, based on systemic toxicity and another expressed in units of mg/L solution, based on direct dermal effects. If two dermal RRVs are available, there may be two HQs, based on exposures expressed in units of mg/kg/day for systemic effects and mg/L solution for dermal effects.

A composite HQ can be derived which takes into consideration all relevant routes of exposure. If all of the RRVs are based on systemic toxicity and the same type of systemic effects are anticipated from all routes of exposure, this composite HQ may be derived simply by summing the HQs for each route of exposure:

$$HQ_{comp} = HQ_{oral} + HQ_{inhal} + HQ_{dermal} \qquad (9)$$

If the effects are route specific, this may not be appropriate and excluding one or more of the route-specific HQs from the composite HQ may be considered. For example, dermal HQs derived from RRVs for dermal effects such as irritation are not combined with other HQs for systemic toxic effects.

When conducting scenario specific risk assessments (for example, workers exposed to a insecticide) HQs are adequate if the exposure estimate is at or below the RRV. If exposure is below the RRV, no adverse effects are anticipated.

If anticipated exposures are above the RRV, some effort must be made to characterize further the nature and likelihood of adverse effects. The NOAEL-uncertainty factor approach does

not explicitly incorporate available data on dose-response or dose-severity relationships, although this kind of information may be available (Figure 2-5). This can be a very serious limitation in assessing risks above the RRV. The dose-severity relationships are not the same for all chemicals and all effects. For some chemicals, the progression from mild to severe effects will be gradual. For other compounds, very few clinically significant effects may be seen in any members of a population until certain systems for detoxication or elimination are saturated. At this point, there may be a very steep rise in the number and severity of effects. Consequently, no general rules can be given for associating an HQ greater than 1 with specific levels of concern.

Depending on the agent and the available data, different approaches are taken to assessing risks above the minimal risk level (MRL). Generally, these approaches use either an explicit dose-response model or a more qualitative assessment of the dose-severity relationship. Specific approaches are detailed in the dose-response assessments for the various agents covered in this risk assessment.

2.6.2. Cancer Risks

For carcinogenic effects, the risk associated with a given scenario and a single route of exposure can be expressed as:

$$P_{life\ span} = SL \cdot D \tag{10}$$

where:
P = *probability of response*
SL = *slope factor*
D = *lifetime average daily dose*

If more than one route of exposure is associated with a carcinogenic response, the risk from all routes can be added:

$$P_{total} = P_{oral} + P_{inhalation} + P_{dermal} \tag{11}$$

As discussed in the dose-response assessment (see section 2.5), a major source of uncertainty is introduced when the exposure duration for the scenario is substantially less than lifetime. This uncertainty cannot be quantified.

2.6.3. Cumulative Exposures

Most scenarios considered in this risk assessment involve exposures that may last for several days to several months. In addition, some program activities may be repeated more than once during a year or for several years during an individual's lifetime. Such exposures are referred to generically as cumulative exposures.

Depending on the specific exposure scenario and the nature of the available data, the consequences of cumulative exposures are assessed in a variety of ways. For carcinogenic effects, as detailed above, total dose is assumed to be related directly to risk. Thus, the consequences of two exposures at a given rate would be twice those of a single exposure.

For toxic effects, concern is triggered by exposures that exceed the RRV. Only a limited amount of most control agents may be applied in a given year. Consequently, most exposure scenarios assume maximum application rates. If the RRV is not exceeded in such applications, it will not be exceeded in multiple applications at lower rates. In addition, cumulative effects for exposures that may last for several months (such as exposure to residues of diflubenzuron) are considered by using RRVs appropriate for chronic or lifetime exposures. If the daily exposure level does not exceed the level that would be tolerable for a lifetime exposure, exposures for shorter periods will not present a hazard. The specific approaches to assessing cumulative effects are discussed in the risk characterization for each agent.

2.6.4. Connected Actions

Individuals are never exposed to a single compound or agent. Some individuals may be exposed to multiple program agents either in their job as applicators or because multiple agents are used to treat the gypsy moth in the area where the individuals live. In addition, all individuals are exposed to a multitude of chemicals and biological organisms every day, in foods, medicines, household products and other environmental chemicals. In this risk assessment, such exposures are generically considered under the term **connected actions**, one or more actions that an individual may take that could affect the individual's risk to the agents used to control the gypsy moth.

There is an immense amount of literature indicating that exposure to multiple chemical or biological agents may lead to toxicologically significant interactions (for example, Yang 1994). For most of the agents under review, however, there is relatively little information pertaining to this issue. The information that is available is included in the risk characterization for each agent. In addition, there is an explicit discussion of the available information in the comparison and summary of risk assessments (section 9) that attempts to characterize the plausible effects of exposure to multiple control agents as well as other common chemicals.

Table 2-1. Risks of dying associated with various activities or mishaps.

Activity/Mishap	1988 Deaths[a]	LLE[a] (days)	Risk per Year[b]	Lifetime Risk[c]
Involuntary risks				
Accidents, all	96,000	366	$3.8 \cdot 10^{-4}$	$2.7 \cdot 10^{-2}$
Motor vehicles	49,000	207	$2.0 \cdot 10^{-4}$	$1.4 \cdot 10^{-2}$
Falls	12,000	28	$4.8 \cdot 10^{-5}$	$3.4 \cdot 10^{-3}$
Poison	5,300	20	$2.1 \cdot 10^{-5}$	$2.5 \cdot 10^{-3}$
Working, all occupations	10,600	60	$4.2 \cdot 10^{-5}$	$1.9 \cdot 10^{-3}$
Falling objects	900	6.0	$3.6 \cdot 10^{-6}$	$2.5 \cdot 10^{-4}$
Air transportation	900	3.7	$3.6 \cdot 10^{-6}$	$2.5 \cdot 10^{-4}$
Electric current	850	4.5	$3.4 \cdot 10^{-6}$	$2.4 \cdot 10^{-4}$
Drowning	800	4.2	$3.2 \cdot 10^{-6}$	$2.2 \cdot 10^{-4}$
Firearms	800	4.2	$3.2 \cdot 10^{-6}$	$2.2 \cdot 10^{-4}$
Water transportation	800	3.3	$3.2 \cdot 10^{-6}$	$2.2 \cdot 10^{-4}$
Railroad transportation	300	1.3	$1.2 \cdot 10^{-6}$	$8.4 \cdot 10^{-5}$
Other transportation	200	0.9	$8.0 \cdot 10^{-8}$	$5.6 \cdot 10^{-6}$
Voluntary risks				
Parachuting		25	$1.8 \cdot 10^{-3}$	$1.8 \cdot 10^{-2}$
Mountain climbing		10	$5.7 \cdot 10^{-4}$	$5.7 \cdot 10^{-3}$
Hang gliding		8	$4.5 \cdot 10^{-4}$	$4.5 \cdot 10^{-3}$
Scuba diving (amateur)		7	$4.2 \cdot 10^{-4}$	$4.2 \cdot 10^{-3}$
Snowmobiling		2	$1.3 \cdot 10^{-4}$	$1.3 \cdot 10^{-3}$
Mountain hiking		0.9	$6.4 \cdot 10^{-5}$	$6.4 \cdot 10^{-4}$
Football, college		0.6	$3.0 \cdot 10^{-5}$	$1.2 \cdot 10^{-4}$
Football, high school		0.3	$1.2 \cdot 10^{-5}$	$4.8 \cdot 10^{-5}$

[a]Estimates are from Cohen 1991. Lost life expectancy (LLE) for involuntary risks are based on exposures of 2,000 hours/year from ages 18–65. For voluntary risk, the LLE is based on engaging in the activity for 1 year.

[b]For involuntary risk, the number of deaths is divided by 250 million, the approximate population of the United States in 1988 (see text for a discussion of limitations). For involuntary risks, the risks are conditional on participation in the activity for 1 year.

[c]For involuntary risks, the duration of risk is assumed to be 70 years except for working, which is assumed to be 45 years. For voluntary risks, the duration of risk is assumed to be 10 years, except for football, which is assumed to be 4 years.

Table 2-2. Severity definitions used in human health risk assessment

Acronym	Definition
NOEL	*No-observed-effect level*: Exposure level at which no biologically or statistically significant effects attributable to treatment.
NOAEL	*No-observed-adverse-effect level*: Exposure level at which effects are attributable to treatment but do not appear to impair the organism's ability to function and clearly do not lead to such an impairment.
AEL	*Adverse-effect level*: Exposure level at which signs of toxicity can be found but must be detected by invasive methods, external monitoring devices, or prolonged systematic observations. Exposure level at which symptoms occur but are not accompanied by grossly observable signs of toxicity.
LOAEL	*Lowest-observed-adverse-effect level*: The lowest exposure level at which an adverse effect has been observed.
FEL	*Frank-effect level*: Exposure level at which gross and immediately observable signs of toxicity are apparent.

Table 3-1. Individuals with skin responses to the gypsy moth in two communities[a]

Factor	Medway (LO)	Lundberg (HI)
Total number of individuals	557	482
Rash during week before infestation	1.1%	1.4%
Rash during first 7 days after larvae emerge	1.6%	10.4%
Extra risk[b]	0.3%	9.5%
Probit for extra risk[b]	2.25	3.67
Touched larvae	8.3%	31.4%
Rash last year not associated with gypsy moth exposure	0.6%	0.8%
Rash where individuals were touched or crawled on by larvae	29.0%	82.0%
Average egg masses/acre	32	3809

[a]Source: Tuthill and others 1984, O'Dell 1994

[b]See section 2 and the glossary for a discussion of extra risk and probits.

Table 3-2. Adverse human health effects associated with exposure to the gypsy moth

Level of Infestation	Egg Masses/Acre	Hazard Quotient	Extra Risk
General Public			
Sparse	50	2	<0.1%-0.2%
Moderate	50-500	20	0.2%-1%
Heavy	500-5000	200	1%-7%
Extreme	20,000	700	13%
Workers and other exposed individuals			
NA	NA	NA	10%-100%

RRV = 30 egg masses/acre

NA = not applicable

Table 2-3. Toxicological assessments related to risk reference values (RRVs)

Acronym	Definition	Methodology Source
	Systemic Toxicity (Noncarcinogenic)	
RfD	*Reference Dose:* Oral dose (mg/kg/day) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.	U.S. EPA 1989a
RfD_s	*Subchronic Reference Dose:* Oral dose (mg/kg/day) not likely to be associated with adverse effects over a less-than-lifetime exposure, in the general population, including sensitive subgroups. [The exposure duration to which this value applies is not clearly defined.]	U.S. EPA 1990a
RfD_{rt}	*Reference Dose for Reproductive Toxicity:* Oral dose (mg/kg/day) not likely to be associated with adverse developmental effects, in the general population, including sensitive subgroups. Used to evaluate effects after single exposure episode.	U.S. EPA 1989a
RfC	*Reference Concentration:* Concentration in air (mg/m^3) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.	U.S. EPA 1990b
MRL	*Minimal Risk Level:* A route-specific (oral or inhalation) and duration-specific estimate of an exposure level that is not likely to be associated with adverse effects in the general population, including sensitive subgroups.	ATSDR 1992
1-Day HA	*1-Day Health Advisory:* A drinking water concentration (mg/L) not likely to cause adverse effects in the general population, including sensitive subgroups, after 1-day of exposure.	U.S. EPA 1989a
10-Day HA	*10-Day Health Advisory:* A drinking water concentration (mg/L) not likely to cause adverse effects in the general population, including sensitive subgroups, over a 10-day exposure period.	U.S. EPA 1989a
TLV	*Threshold Limit Value:* An air concentration (mg/m^3) not likely to cause adverse effects in exposed workers, over a normal period of work.	ACGIH 1991
	Carcinogenicity	
Slope Factor [q_1^*]	*Cancer Potency Parameter:* A model-dependent measure of cancer potency $(mg/kg\text{-}day)^{-1}$ over lifetime exposure. [Often expressed as a q_1^* which is the upper 95% confidence limit of the first dose coefficient (q_1) from the multistage model.]	U.S. EPA 1987a
Unit $Risk_{air}$	*Unit Risk for Inhalation Exposures:* The risk associated with a continuous lifetime exposure to an air concentration expressed $(mg/m^3)^{-1}$ or $(\mu g/m^3)^{-1}$.	U.S. EPA 1987a
Unit $Risk_{water}$	*Unit Risk for Water Consumption:* The risk associated with a continuous lifetime exposure to a drinking water concentration expressed $(mg/L)^{-1}$ or $(\mu g/L)^{-1}$.	U.S. EPA 1987a

Table 2-4. Uncertainty factors (UF) used to derive risk reference values (RRVs)*

Definitions		Use Summary		
Factor	Basis	This Assessment	ATSDR	U.S. EPA
Interhuman	Use a 10-fold factor when extrapolating from valid experimental results using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among humans.	Yes	Yes	Yes
Experimental to human	Use a 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies on human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to humans. If adjustments to the dose metameter are adequate, this factor can be reduced or eliminated.	Yes	Yes	Yes
LOAEL to NOAEL	Generally use a 10-fold factor when deriving an RRV, RfD, or MRL from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs.	Yes - UF Varies	Yes - UF always 10	Yes -UF varies
Subchronic to chronic	Generally use a 10-fold factor when deriving an RRV or RfD from less than chronic results on experimental animals or humans. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs.	Yes	No	Yes
Modifying factor	Use professional judgment to determine an additional uncertainty factor that is >1 and ≤ 10 for deriving an RRV or RfD. The magnitude of the MF depends upon the professional assessment of the scientific uncertainties of the study and data base not explicitly treated above. The default for the MF is 1	Yes	No	Yes
Incomplete database	Generally use a 10-fold factor when deriving an RRV or RfD from valid results in experimental animals when the data are "incomplete." This factor is intended to account for the inability of any study to address all possible adverse outcomes.	Sometimes	No	Yes

*Source: ATSDR 1992

Table 2-5. Comparison of various dose-response models for the data illustrated in Figure 2-5.

Name	Description[a]	b	m	r^{2b}	p[c]	Risk at a dose of 0.001
Linear	$P = m D + b$	0.032	0.012	0.9978	0.0011	$3.3 \cdot 10^{-2}$
Multiplicative	$P = b D^m$	-3.1	0.60	0.9692	0.0155	$1 \cdot 10^{-10}$
Exponential	$P = e^{(b+mD)}$	-2.7	0.055	0.9049	0.0487	$6.5 \cdot 10^{-2}$

[a]**P**=probability of response.
D=dose
m=slope
b=intercept

[b]r^2 = proportion of the variability in the data accounted for by the model.

[c]**p** = Probability that the slope, **m**, is significantly different from 0.

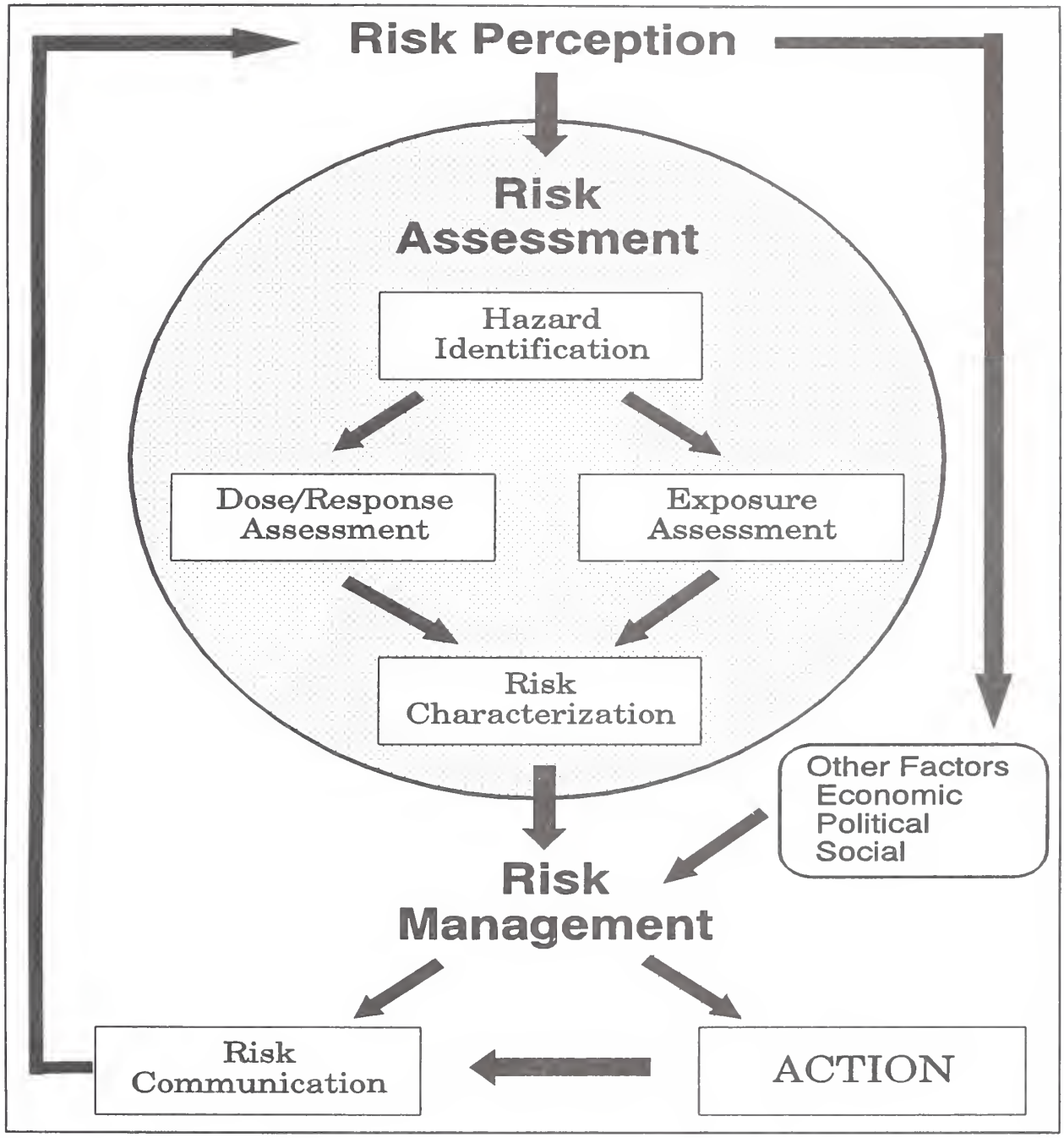


Figure 2-1. Risk Assessment Overview. The risk assessment process supports risk management activities, which may include actions to decrease risk and communicate risk to the general public or to officials who are responsible for controlling or decreasing risk.

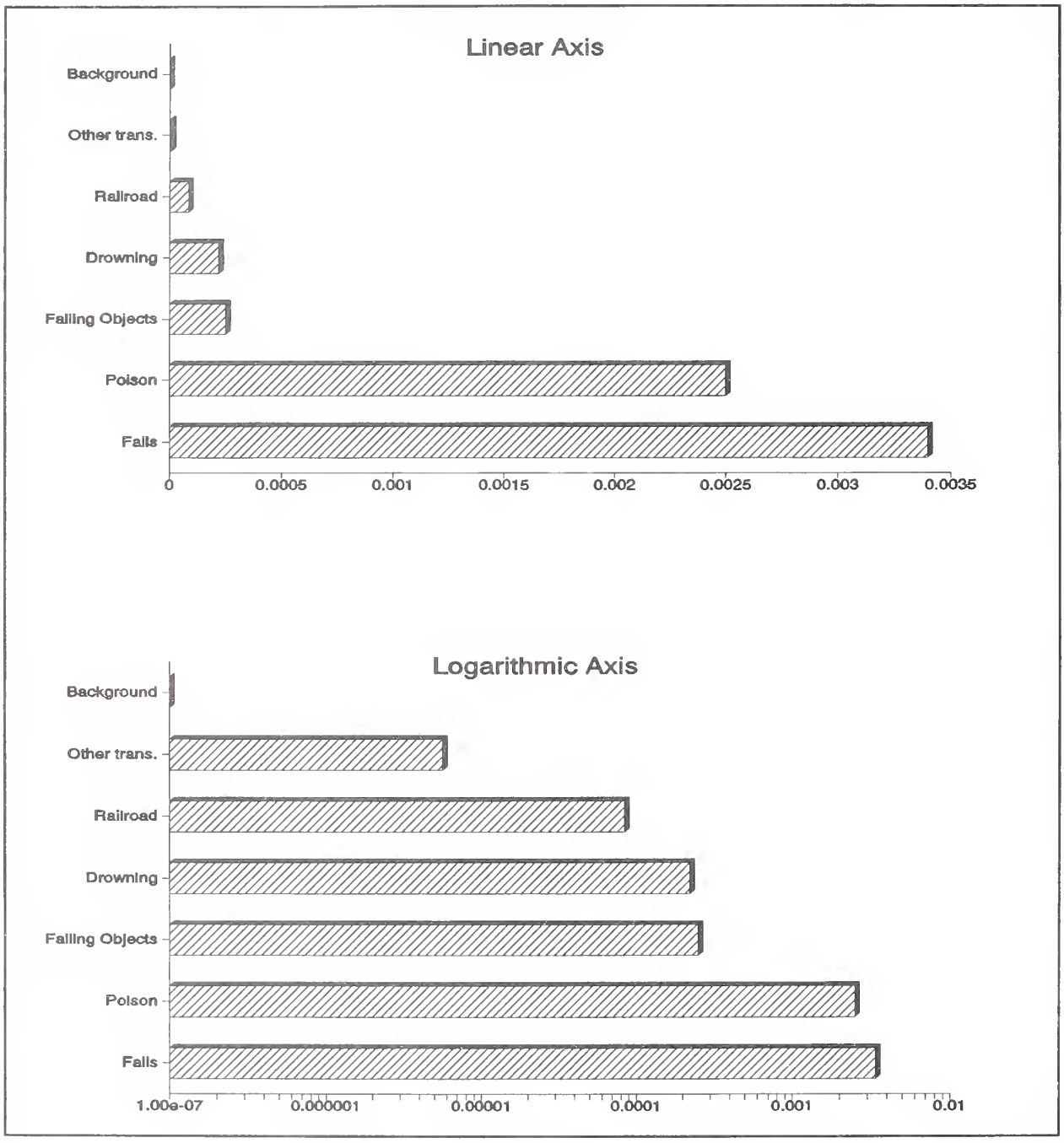


Figure 2-2. Comparison of Common Lifetime Risks of Mortality (see Table 2-1 for data). Common risks are plotted with two types of axes, linear and logarithmic. Linear axes are common and intuitive. Equal distances on a linear axis represent equal differences in values. Logarithmic axes can be very useful for illustrating differences in numbers that encompass a wide range of values but are somewhat less intuitive. Equal intervals on a logarithmic or log scale represent equal ratios.

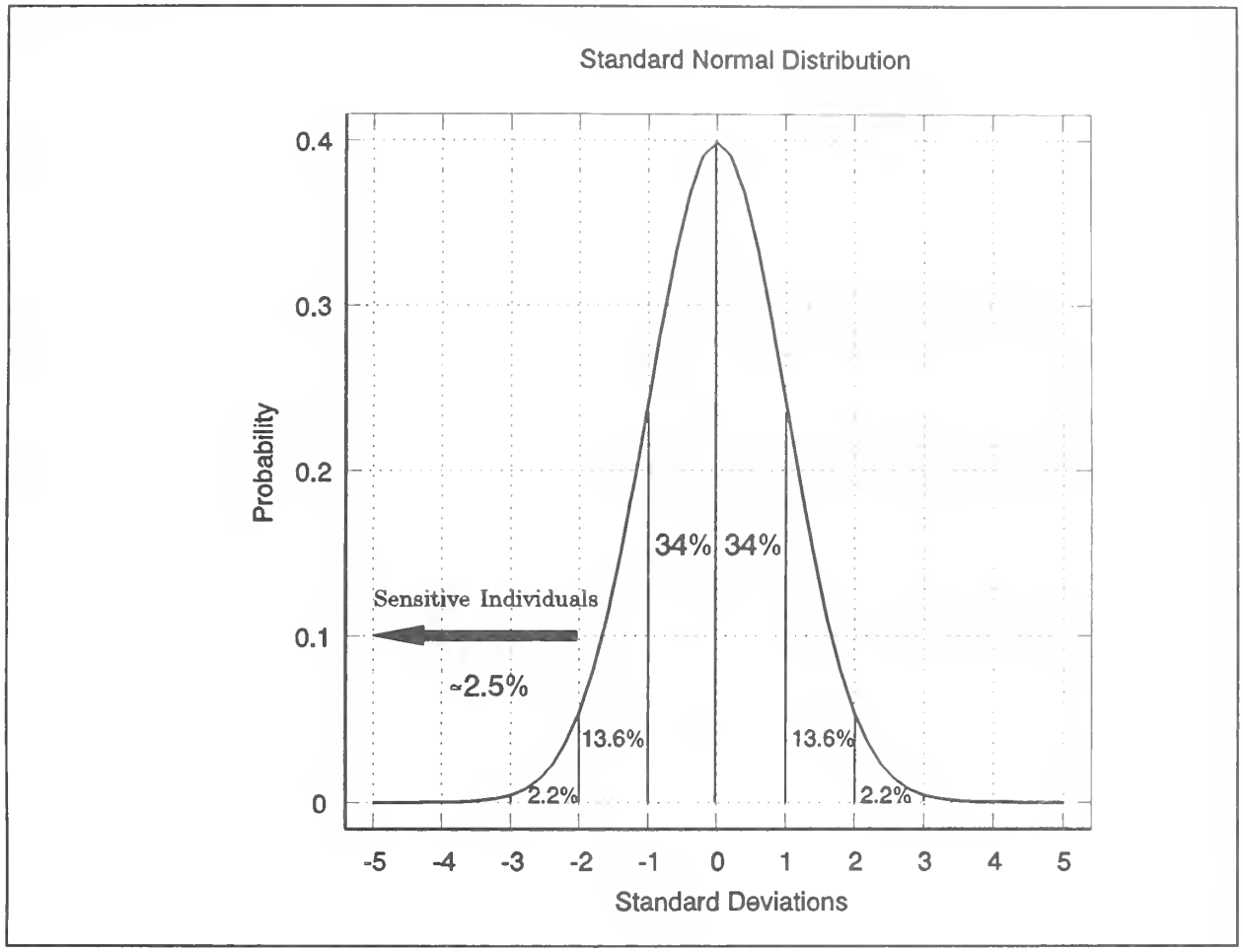


Figure 2-3. Sensitive Individuals in a Normal Distribution of Tolerances. In any normal distribution of tolerances, some individuals will be more sensitive than others. Although those individuals may be termed **sensitive**, they do not constitute a sensitive subgroup because they are not qualitatively different from other members of the population. (See Figure 2-4 for an illustration of sensitive subgroups.)

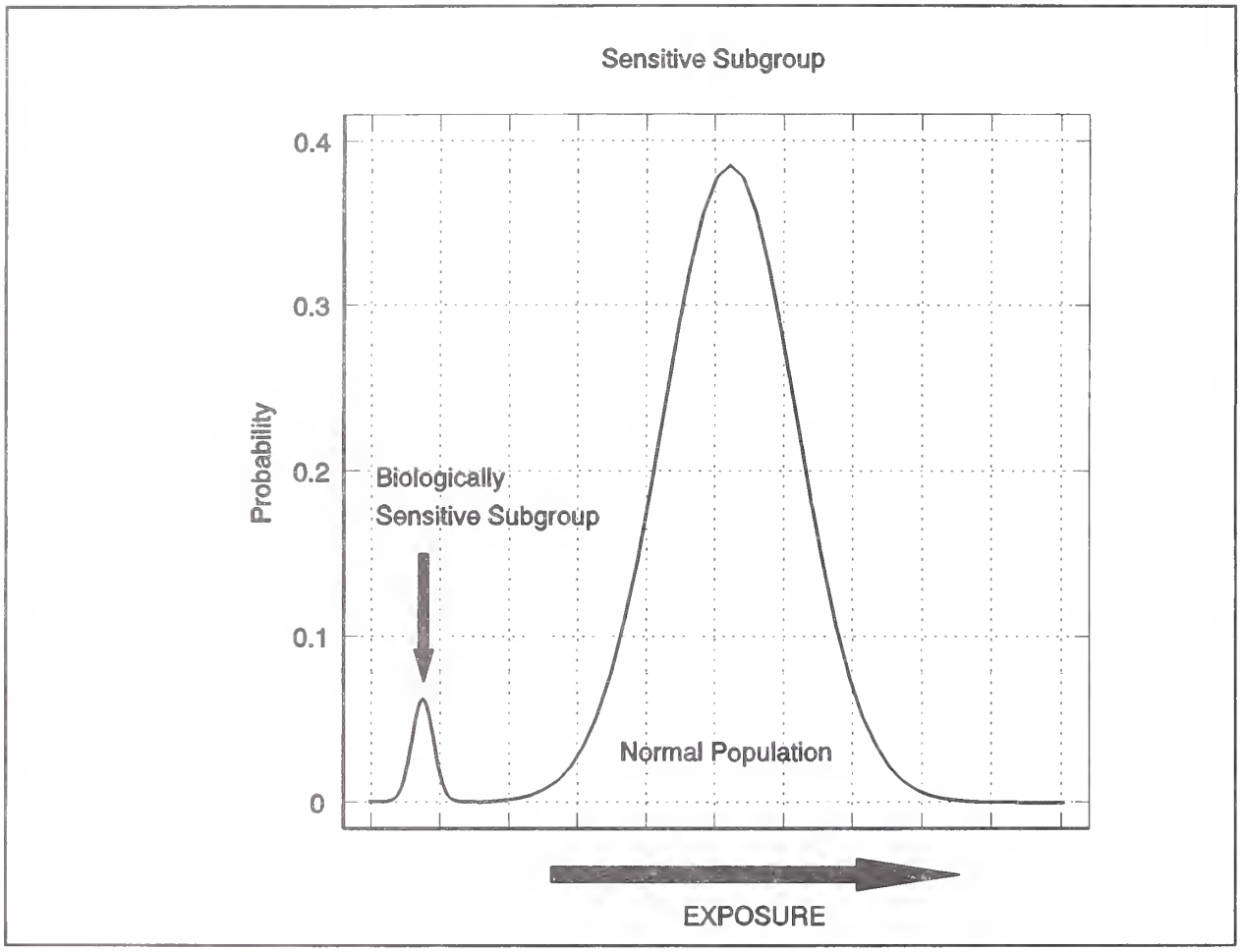


Figure 2-4. Sensitive Subpopulation. The large bell-shaped curve represents the normal population (see figure 2-3); the smaller bell-shaped curve represents the biologically sensitive subgroup. This pattern indicates that a group of individuals is in some way biologically different because their extreme sensitivity cannot be described by a **normal** distribution in the statistical sense.

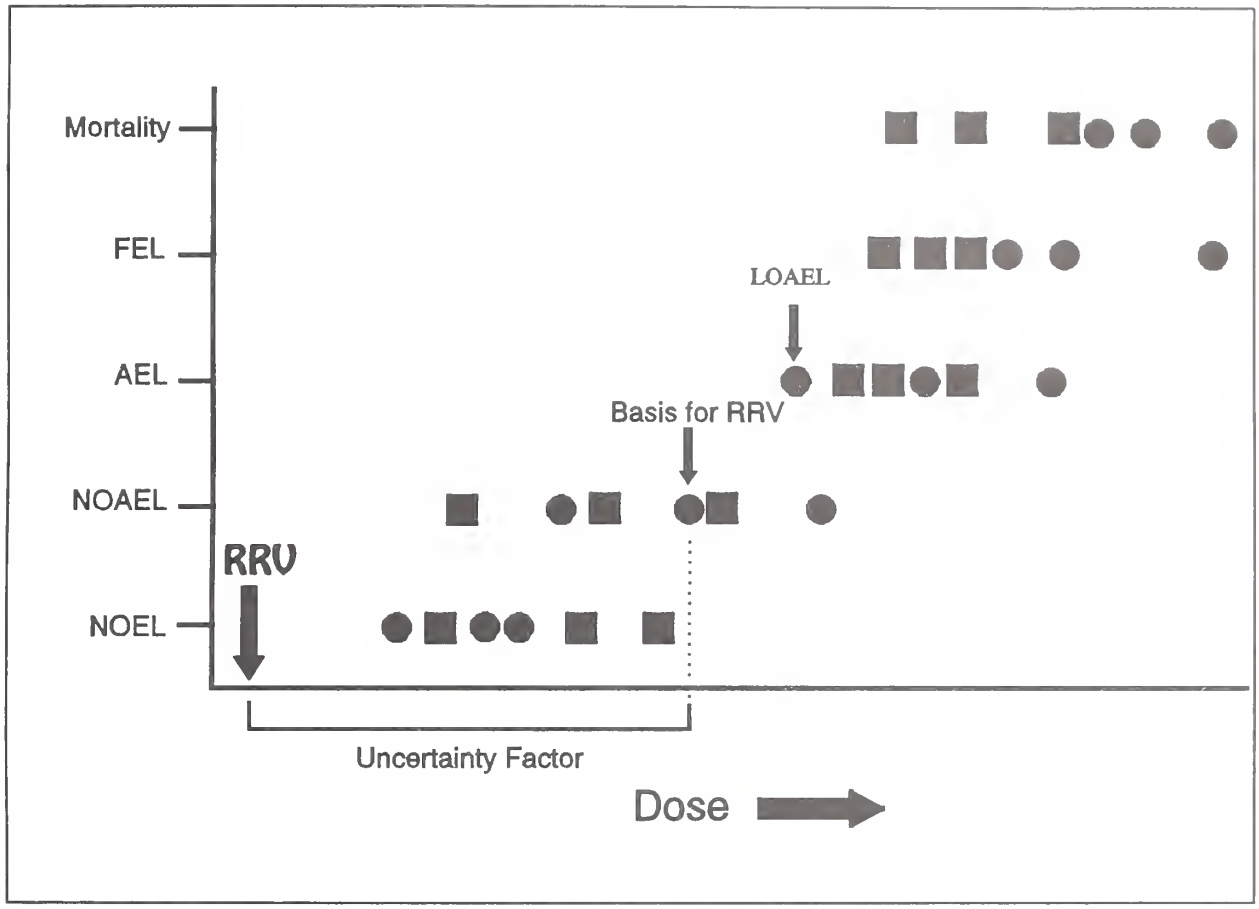


Figure 2-5. Overview of RRV Derivation. Hypothetical dose-severity data are plotted for two effects, designated by circles and squares. The effect designated by circles is the most sensitive effect because it has the lowest AEL (LOAEL). Once the appropriate NOEL, NOAEL or LOAEL is identified, one or more uncertainty factors are applied to estimate the RRV or other level of acceptable exposure.

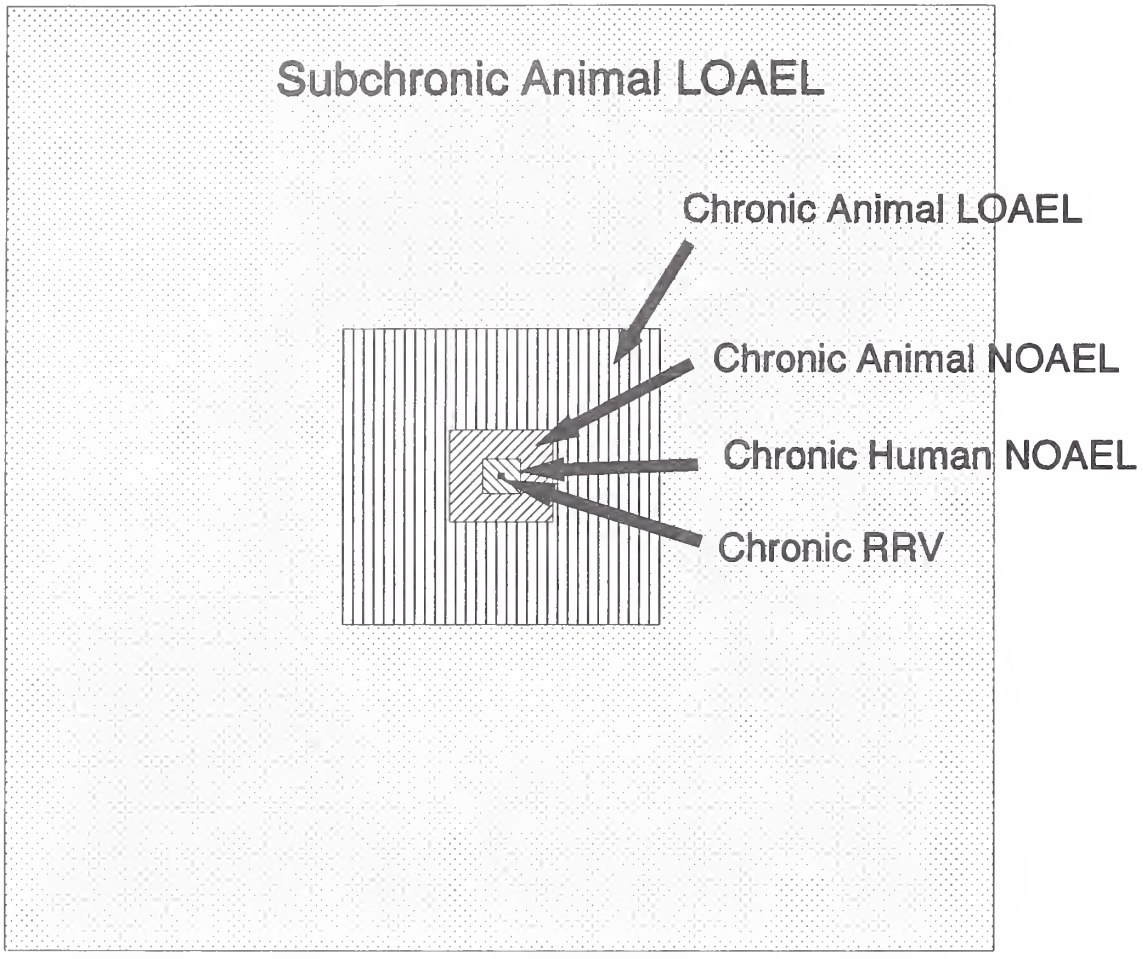


Figure 2-6. Relationship of Experimental Data to RRVs. Depending on the nature of the experimental NOAEL or LOAEL and the RRV being derived, the relationship of the experimental data to the RRV may be remote. This figure illustrates the most extreme case, the use of a subchronic LOAEL to estimate a chronic RRV.

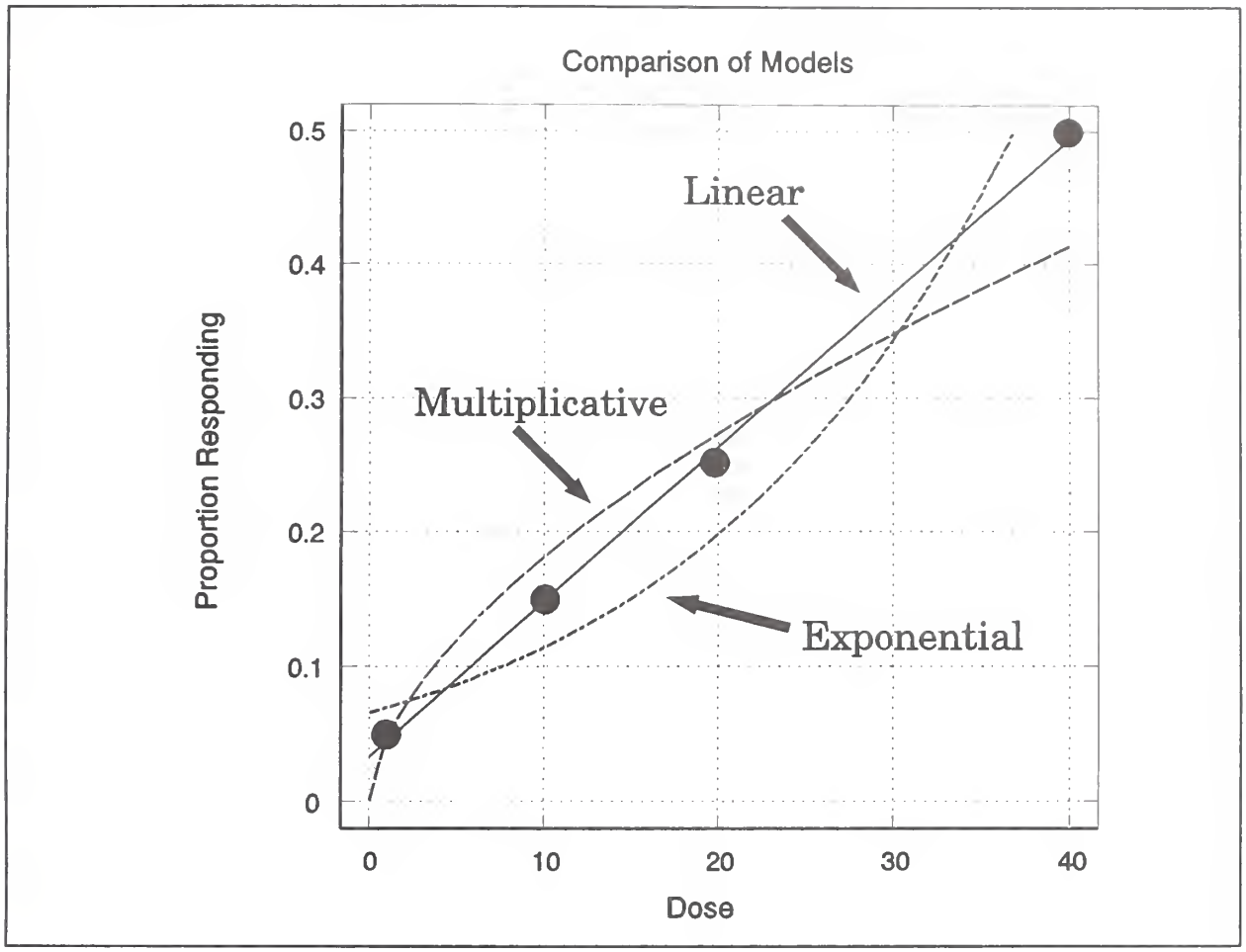


Figure 2-7. Comparison of Dose-Response Models. Within the observable range, most reasonably flexible models give satisfactory fits to most reasonable data sets. The simple linear model best fits the available data. Nonetheless, the other two-parameter models, the multiplicative and exponential model, also fit the data well--the r^2 is greater than 0.9 and the p-values are less than 0.05--even though the shapes of these models differ substantially from one another and from the shape of the linear model.

3. Gypsy Moth

3.1. Gypsy Moth Infestations

On four continents (Asia, Africa, Europe, and North America), various strains of the gypsy moth, Lymantria dispar, are well-known defoliators of forest and shade trees. Although the insect is not native to North America and was known to be a serious forest pest in Europe, the European strain of the gypsy moth was brought to this continent deliberately. In 1868 or 1869, near Boston Massachusetts, it escaped. The gypsy moth has spread steadily since that time. By 1974, the gypsy moth was established in much of New England, New York, New Jersey, and Pennsylvania, with isolated pockets in Michigan (Campbell 1979). By 1989, the infestation covered much of the northeastern United States (Virginia to Michigan to Maine) as well as southern Quebec and Ontario (Nealis and Erb 1993). While the gypsy moth population on the east coast of North America has been long established in a contiguous territory, infestations on the west coast and mid-western region of North America are isolated in relatively small geographical areas. The first gypsy moth on the west coast was identified in California in 1973. Since then, other isolated infestations have been reported in California, Oregon, Washington, and British Columbia (Cram 1990). The APHIS database on gypsy moth eradication efforts lists 26 states in which isolated infestations have been noted.

The life cycle of the gypsy moth is described in several reviews (for example, Abrahamson and Klass 1982, Cram 1990). In the northeast, the adult female lays eggs in July or August in masses of 100–1,000 eggs/egg mass in a protected area. The larvae or caterpillars go through various stages, referred to as instars. In the northeast, first stage larvae (first instars) hatch in early to late May and go through five additional larval stages between May and late June. This process occurs somewhat earlier in the southeast. The transition from each stage to the next involves molting, during which time the caterpillar sheds its outer skin. It is during the larval stages that feeding occurs. Gypsy moth larvae have definite food preferences: oak, birch, and apple trees are their favorite sources of food. Other species such as beech, maple, and white pine are less favored. Hemlock and pitch pine seldom serve as food sources, and species such as black locust and white ash are generally avoided (Campbell 1979). First instars spin fine silk threads near the tops of trees from which they suspend themselves. After the thread breaks, the larvae can be transported over relatively long distances by the wind. Between late June and mid-July, the caterpillars spin sparse silken cradles and form pupae. After 7–14 days of pupation, the adult moths emerge and mate, and the life cycle is repeated.

3.2. Hazard Identification

3.2.1. Overview

In addition to the well-documented effects that the gypsy moth has on the environment, gypsy moth infestations are associated with adverse human health effects, including skin lesions, eye irritation, and respiratory reactions. Gypsy moth infestations may also be a nuisance. Although the nuisance issue may not constitute a frank or easily measured health effect, the available literature suggests that gypsy moth infestations may cause marked psychological stress in some individuals. In extreme infestations, surface water may be contaminated with gypsy moth frass (larval excrement). In some cases, the level of contamination may be sufficient to affect water quality. The contamination can occur not only because of the gypsy moth frass on the surface water, but also because degradation of the vegetative canopy will increase water runoff.

3.2.2. Dermal Reactions

Dermal reactions to contact with lepidopteran larvae are relatively common (Hellier and Warin 1967, Katzenellenbogen 1955, Perlman 1965, Schmidt 1982, Wirtz 1984). Moreover, these reactions are the most well characterized and easily quantified health effect caused by gypsy moth infestations. A late 19th century document describes a situation in which an individual in Medford Massachusetts "... was poisoned by them [gypsy moths]. While killing them upon the trees they would get upon his neck and blister and poison it" (Forbush and Fernald 1896 p. 16). A few years later, a physician in Boston reported a number of cases of "inflammation of the skin, which were undoubtedly caused by contact with some caterpillar ... which must be some recently introduced species" (White 1901 p. 599). Although Dr. White attributed these cases to the brown-tailed moth (Euproctis chrysorrhea), they are consistent with the reported effects of exposure to the gypsy moth, which had been released in the Boston area some years before. The literature contains no further mention of human health effects associated with the gypsy moth for almost a century.

In the early 1980s, there was a massive gypsy moth infestation in the northeastern part of the United States. In 1981, outbreaks of itchy skin rashes that coincided with the heavy infestations in the northeast were widespread and a source of public annoyance (Marshall 1981). Coincident with this infestation, reports describing the human health effects associated with exposure to the gypsy moth appeared in the medical literature.

The skin reactions seem to be caused by contact with the larval setae, small fine hair-like protrusions from the body of the larva (Allen and others 1991). The larva has four kinds of setae, two of which are hollow and attached to glandular cells. The hollow setae are suspect, but not unequivocally identified as the setae associated with skin reactions in humans

(Anderson and Furniss 1983). According to several case reports and epidemiology studies, dermal effects in humans are usually associated with exposure to the first instars (Anderson and Furniss 1983, Tuthill and others 1984). Nonetheless, whole first instars and the setae of fifth instars contain histamine (Shama and others 1982), a compound that causes wheals, which are characteristic of dermal contact with gypsy moth larvae (Sullivan 1982).

The mechanism (or mechanisms) by which the dermal effects are produced is not well characterized. Three kinds of reactions, including mechanical irritation, toxic reaction to a compound such as histamine, and an immediate or delayed allergic reaction, are proposed in the literature (Burnett and others 1989, Shama and others 1982). An allergy to the gypsy moth is suggested by the work of Beaucher and Farnham (1982). Closed patch tests were conducted on 8 individuals who had a history of skin reactions to the gypsy moth and 11 individuals, with no such history, who served as controls. A positive response to the patch test was observed in each of the individuals who had a history of skin reactions to the gypsy moth and in only one individual in the control group. The observed response was consistent with the reported dermal effects of gypsy moth exposure. In some cases, severe itching (pruritis) kept individuals awake at night. In general, the time from exposure to the onset of the reaction was 24–48 hours, suggesting a delayed hypersensitivity similar to poison ivy reactions. In another study, 10 of 17 workers at a laboratory conducting research on the gypsy moth reported a history of adverse skin or respiratory reactions. According to the results of scratch tests, 7 of the 10 workers who reported a history of adverse reactions were allergic to gypsy moth parts or other substances. The intensity of the response, based on a categorical classification of skin responses, was greater for extracts of cast larval skins and whole larvae than for egg mass hairs (Etkind and others 1982).

Wheals are the most characteristic skin lesions associated with human contact with the larvae. These wheals, resembling the raised patches of skin often associated with mosquito bites, may be approximately 0.25–0.5 inches in diameter and are surrounded by an area of redness (erythema). In severe cases, the wheals may be so numerous that they overlap on large areas of the skin, a condition referred to as urticaria. Contact with the larvae also has caused contact dermatitis, characterized by a rash rather than wheals (Anderson and Furniss 1983). These two types of skin lesions, wheals and rashes, may be parallel to two human health effects associated with gypsy moth exposures: a toxic response and an allergic response. Both lesions may result in pruritis. These effects can persist for several days to 2 weeks and often require medical treatment (Aber and others 1982, Allen and others 1991, Shama and others 1982).

During the severe infestations in the early 1980s, there were three published reports regarding the development of skin reactions in school children (Aber and others 1982, Anderson and Furniss 1983, Tuthill and others 1984).

In the spring of 1982, a telephone survey was conducted to collect information from approximately 1,000 people (representing more than 90% of those selected for study) in one highly infested community (HI, Lundberg) and one minimally infested community (LO,

Medway) in Massachusetts (Tuthill and others 1984). The risk of developing a dermal response over a 1-week period was 10.4% in the HI community and 1.6% in the LO community. The responses occurred most often in individuals who had developed rashes during the previous year or who had direct contact with the larvae (that is, larvae crawled on them). The combination of these two factors resulted in an additive increase in risk. Other variables related to increased response included a history of hay fever and the practice of hanging clothes outdoors to dry. The rates at which the dermal responses developed in individuals in the HI community were inversely associated with age (18.8% in 0- to 12-year olds, 10.2% in 13- to 59-year olds, and 2.1% in 60-year olds and older individuals). The average prevalence of dermal responses in both communities combined, 1 week before the emergence of the first instars, was 1.3% (Tuthill and others 1984).

Information regarding population densities of the gypsy moth in the two communities is not presented in the study; however, one of the coauthors of the study surveyed egg masses in the two communities (O'Dell 1994). In the high exposure community, surveys were conducted on 27 0.1-acre plots throughout the infested area between October 5 and 6, 1981. The number of egg masses counted at each site ranged from 0 to 1,000, with an arithmetic mean of 380 egg masses/site. Egg masses were detected at all but one site. The average egg mass density was approximately 3,800 masses/acre. In the LO exposure community, 20 sites were surveyed. The arithmetic average number of egg masses per acre was 32, but the egg masses were unevenly dispersed. No egg masses were found at 15 of the 20 sites, and egg mass counts at the other 5 sites were 2, 2, 3, 7, and 50. All of these sites were located at the western end of the community. These egg mass counts were made in the fall, before the outbreak of rashes in the following summer. The use of these egg mass densities as a surrogate for estimating exposure to larvae is based on the assumption that there is a positive correlation between the number of viable larvae in the summer and the number of egg masses in the preceding fall. Occasionally, below normal midwinter temperatures have resulted in high mortality among overwintering eggs (Bess 1961). Usually, however, fall egg mass counts are closely related to subsequent larval density, particularly among early instars.

Sometime between the end of April and the third week of May, 1981, there was an increased incidence of rashes among students in two schools in Northeast Pennsylvania (Aber and others 1982). School A had a response rate of 42.2% (135 of 320 students), and school B had a response rate of 25.3% (76 of 300 students). The dermal responses included pruritic rash and occasional urticaria, usually located on exposed areas of the body. Based on a survey of a group of students from the same schools who were not affected by the gypsy moth, these investigators determined that there was a statistical association between touching larvae ($p < 0.01$), working in a garden ($p < 0.05$), or going fishing ($p < 0.01$) and the incidence of rashes.

Concurrent with the infestation in Pennsylvania was an infestation in Connecticut, associated with an outbreak of skin reactions in students at several schools within the community (Anderson and Furniss 1983). Urticaria was observed in 7.2% of the 2,600 students

attending four schools in Newton, Connecticut. More than 50% of the cases of urticaria occurred during the first week in May, coinciding with the emergence of first instars. Very few cases (approximately 10) occurred during the third week of May when the larvae were predominantly in the third instar. In Burlington, Connecticut, the incidence of skin reactions was approximately 5.1% (96 of 1,870). In another school, about 7.1% (75 of 1,058) of students were affected. In Bristol, Connecticut, there were 1,348 cases of rashes in the public schools, amounting to approximately 10.7% of the total student enrollment (12,500). Health officials estimated that the true prevalence may have been 3 times higher than reported; however, details supporting this assessment were not provided. Nonetheless, the estimate is consistent with the occurrence of rashes in 12 of 25 children attending a nursery school in the same community.

3.2.3. Ocular and Respiratory Effects

The ocular and respiratory effects in humans after exposure to the gypsy moth or other lepidopteran larvae are less well documented, compared with dermal effects. Of the 10 workers with a history of adverse reactions to the gypsy moth (Etkind and others 1982), all 10 had skin reactions, 4 had eye irritation, and 2 had respiratory reactions. In a survey of laboratories conducting research on insects, 28.7% of all reported allergies were attributed to the gypsy moth. The most frequent reactions among affected individuals were skin irritation (61%), sneezing or runny nose (67%), and eye irritation (60.9%). Labored respiration was observed in 33% of the affected individuals (Wirtz 1980). The frequencies of these reactions are for all individuals who had adverse health effects after exposure to insects in general, not just the gypsy moth.

NIOSH is conducting an epidemiology study of workers involved in the rearing of insects, including the gypsy moth (Petsonk 1994). Although the results of this study are not available yet, discussions with the investigators suggest that this study will be useful for further characterizing the nature of dermal, ocular, and respiratory effects of exposure to the gypsy moth, but will not include the data necessary for making a quantitative risk assessment for general public or worker exposure.

The severity of ocular or respiratory effects in humans after exposure to the gypsy moth is not well characterized; however, these effects appear to be reversible. Although some respiratory effects may involve pain, there are no data to indicate that the respiratory effects are life threatening or require hospitalization (Perlman 1965, Shama and others 1982).

3.2.4. Other Effects

The stress or anxiety associated with gypsy moth infestations is difficult to assess. This stress cannot be associated with frank health effects. In many communities, the stress may be exacerbated by disputes about appropriate approaches for dealing with the pest (Williams,

1982). Anecdotal reports suggest that some people may be extremely anxious about infestations (National Gypsy Moth Management Group 1991 p. 3):

> ... the mere mention of insects sends some people into fits of scratching, but phobia was not an adequate explanation for the epidemic of runny noses, irritated eyes, and rashes that happened to coincide with the occurrence of gypsy moth caterpillars last spring [1990]. Every [Pennsylvania] county and state gypsy moth office received numerous calls and one agency was reported to have received over 2,700.

Moreover, reports regarding the willingness of populations to pay for gypsy moth control (Miller and Lindsay 1993a and 1993b) suggest that gypsy moth infestations are regarded as highly undesirable by the general public, both in terms of aesthetic damage and the potential for adverse effects on human health. Among 629 individuals residing in infested areas, the most frequent reasons for a willingness to pay for control measures against the gypsy moth were aesthetic damage (15%) and the nuisance factor (13%) (Miller and Lindsay 1993b). Concerns regarding adverse health effects directly related to exposure were expressed by only 4% of the responders.

In most instances, gypsy moth defoliation will have little effect on adjacent water bodies (Corbett and Lynch 1987, Grace 1986). During heavy infestations, water quality may be affected by increased runoff and by direct contamination with frass. During active defoliation, fecal streptococci levels in stream water have been as high as 25,000/100 mL and fecal coliform densities have exceeded 90/100 mL (Corbett 1992). There have been no reports of adverse effects on human health associated with changes in water quality, but such effects seem plausible.

3.3. Exposure Assessment

Gypsy moth populations can be monitored by estimating the numbers of egg masses, larvae, or adults. For adult moths, population surveys usually involve the use of pheromone traps with or without an insecticide, as discussed in sections 7 and 8 of this risk assessment. Surveys of larval populations may involve band trapping, direct examination, or correlations between frass volume and population density. The most accurate method of estimating established gypsy moth populations is by counting egg masses in direct field sampling (Fleischer and others 1992, Nealis and Erb 1993).

The population dynamics of the gypsy moth are extremely complex. Depending on pest density and outbreak duration, gypsy moth populations are influenced by vertebrate and invertebrate predators, insect parasites, fungal, bacterial, and viral pathogens, availability of favored food species, biochemical changes in host foliage induced by prior defoliation,

dispersal characteristics of the pest, competition for food, and weather (Campbell 1981, Elkinton and Liebhold 1990).

As long as gypsy moth populations remain sparse, the larvae usually eat only a small proportion of the foliage of even their most favored host species, and contacts with people are rare. In general, predators play their most important role when gypsy moth populations are in this innocuous phase. Densities in such populations generally are not greater than 50 egg masses/acre.

For several years, gypsy moth populations may exist in a density range high enough to make the insect a minor nuisance in wooded communities and cause partial defoliation. Insect parasites may play their most important role in this intermediate range (Liebhold and Elkinton, 1989). Typical population densities at this stage may vary between about 50 and 500 egg masses/acre.

Once the gypsy moth population increases to a full-scale outbreak, the combination of insect frass and leaf fragments, loss of shade at midsummer, and the large number of larvae may become a major nuisance (Williams 1982). Although the duration of such outbreaks is unpredictable, the principal factors that influence the pest include a variety of pathogens, intraspecific competition for food, and inclement weather (Campbell 1981, Podgwaite 1981, Miller and others 1989). During such outbreaks, typical densities usually range between about 500 and 5,000 egg masses/acre, although densities greater than 20,000 egg masses/acre are occasionally recorded.

Egg mass densities in infested areas tend to be lower in areas where the human population is dense, compared with less densely populated areas. At the forest periphery, however, egg mass densities can be much higher and seem to be associated with man-made objects (Campbell and others 1976). Within a relatively limited geographical range, egg mass densities may vary remarkably. For instance, in a heavily infested area with a mean egg mass density of approximately 3,800 egg masses/acre, egg mass counts ranged from 0 egg masses/0.1 acre surveyed to 1,000 egg masses/0.1 acre surveyed (O'Dell 1994). Similar variability in egg mass density has been observed in larger survey areas, as well (Reardon and others 1993). During a heavy infestation, as many as 50,000 larvae may inhabit a single tree. In such extremely dense concentrations, the generation of frass may be sufficiently intense to be audible, sounding like a light rain (Beaucher and Farnham 1982).

Given this relatively localized variability in insect populations, quantitative estimates of the potential for human exposure cannot be made. Epidemiology studies conducted in gypsy moth infested communities suggest that standard measures of exposure intensity may not be meaningful, even if they could be made. The most important factor may be the probability of coming into contact with one or more larvae, rather than the number of larvae in a population. In this respect, patterns of human behavior, such as the amount of time spent outdoors and certain kinds of activities likely to result in contact with larvae may be more important than measurements of the local larval population. As the density of the larval

population in an area increases, exposure is likely to increase; however, more precise relationships of larval population density to human exposure are not possible.

3.4. Exposure-Response Assessment

The data from the three available reports regarding skin reactions in school children during gypsy moth infestations (Aber and others 1982, Anderson and Furniss 1983, Tuthill and others 1984) are useful for estimating the number of responses during relatively severe infestations; however, only one of the studies (Tuthill and others 1984 as supplemented by data from O'Dell 1994) is useful for constructing an exposure-response relationship.

Two kinds of exposure-response assessments can be made using the available data. The first is based on the standard RRV approach (that is, an exposure level associated with no adverse effects in an exposed population). The second relates the gypsy moth population density (using egg masses per acre) to the prevalence of skin reactions in the human population. Both types of estimates are based on data from Tuthill and others (1984) with supplemental data from O'Dell (1994) (Table 3-1).

For the RRV approach, the Medway community, (that is, the LO exposure group) may be considered a NOAEL because the incidence of skin responses during the week after emergence (Table 3-1, row 3) is not significantly higher than in the week before emergence (Table 3-1, row 2), using McNemar's test for correlated proportions (Everitt 1977). The exposure associated with this response is 32 egg masses/acre. Because sensitive subgroups are likely to have been encompassed by the populations considered in the study, no uncertainty factor is applied to the egg mass density, and the RRV is taken with one significant digit at 30 egg masses/acre.

The quantitative relationship of dermal response to egg mass density can be based on probit analysis (section 2). The measure of exposure is egg masses per acre. To apply this method to the data from Table 3-1, the incidence of skin rashes during the week of emergence must be corrected for some underlying background rate. That is to say that skin rashes occur for a variety of reasons and not all rashes reported in the week of emergence should be attributed to gypsy moth exposure. The study by Tuthill and others (1984) provides two kinds of data that can be used to make this correction, the rates at which rashes occurred the week before the emergence of the gypsy moth (Table 3-1, row 2) and the rates at which rashes occurred the previous year (Table 3-1, row 7). Rates from the week before are used because they are more likely to reflect the natural background rate, given that other allergens coexisted with the emerging larvae. Using these rates, extra risk can be calculated as:

$$P_E = \frac{P_O - P_B}{1 - P_B} \quad (12)$$

where P_E is defined as the extra risk, P_O is the observed response (row 3), and P_B is the estimate of the background response not associated with the agent (row 2). The extra risk, expressed as percent response, is then converted to probits, which are estimations of the number of standard deviations that the response rate is from the population mean or 50% response (see section 2). These conversions are given in row 5 of Table 3-1. With these conversions, the relationship of probit response (Y) to log egg mass per acre (EM) is:

$$Y = 0.68 \log(EM) + 0.94 \quad (13)$$

This relationship is useful for assessing the effect of exceeding the RRV. It must be emphasized, however, that this equation is based on only two points. Since two parameters are estimated, there are no degrees of freedom; hence, the errors in these estimations cannot be characterized (see section 2.5).

The study by Tuthill and others (1984) is useful also for estimating the probability of response after exposure to the larvae. Based on the ratio of the response rates (row 3) to the reports of touching the larvae (row 6), this probability is 20% for Medway (LO) and 33% for Lundberg (HI). The somewhat higher rate in the heavily infested area suggests that larvae in more dense populations may be more effective, for some reason, in causing rashes in humans (Tuthill and others 1984).

3.5. Risk Characterization

As discussed in the hazard identification (see section 3.2), exposure to gypsy moth larvae is associated with dermal, ocular, and respiratory effects in humans. In addition, infestations are often considered to be a nuisance and cause aesthetic damage to the environment. Both of these factors can lead to stress in some individuals. Also during severe infestations, water quality may be affected. Of these effects, skin reactions are most readily amenable to quantification. This may also be considered the most sensitive effect. That is, if exposure levels are less than levels at which a substantial increase in skin irritation is observed, other effects are not likely to be seen.

3.5.1. Uncertainties

Although there is no uncertainty that humans exposed to early stage gypsy moth larvae are likely to have adverse health effects including skin lesions, eye irritation, and respiratory responses, most of the available studies are not directly applicable in a quantitative risk assessment. Risk of human exposure to the gypsy moth is associated with the probability of

coming into contact with an early instar. This probability, in turn, is related to the density of the human and gypsy moth populations as well as the habits of the individuals in the infested areas. Limited data suggest that the prevalence of skin reactions is greatest among young children (Tuthill and others 1984). This finding may indicate that children are more sensitive than adults to the effects of exposure, and it may reflect the fact that children spend more time outdoors. Because of the interrelationship of gypsy moth population density and human behavior to exposure, two types of probabilities are of concern to this risk assessment. The first type of probability is conditional: the chance that an individual will have a toxic response if contact is made with a gypsy moth larva. This probability is likely to be related to the sensitivity of the individual to the gypsy moth as well as to the magnitude of contact (that is, frequency, duration, and amount). The second type of probability is population risk: for a given level of infestation, the proportion of the human population likely to be affected.

The exposure-response assessment is based on one epidemiology study in which only two communities were monitored. Although this is adequate for the definition of a standard RRV, the application of these data to an exposure-response model is tenuous because errors associated with the estimates cannot be characterized.

Egg mass density is the only available measure of exposure in the study on which the risk assessment is based. This is used as a surrogate for exposure to early instar larvae. A variety of factors may influence the relationship of egg mass density to the number of early instars, which increases the uncertainty in the risk assessment.

As with any exposure-response or dose-response assessment, the selection of a dose-response model is somewhat arbitrary and adds another element of uncertainty. Probit analysis is only one of several models that might be applied. This factor is relatively insignificant for infestations between 30 and 300 egg masses/acre, which encompasses levels usually noted during mild to moderate infestations, because little extrapolation is necessary (see section 2.5). Consequently, most exposure-response models would yield similar estimates of risk. As discussed in the hazard identification (see section 3.2), the gypsy moth may exert irritant effects by more than one mode of action. If this is the case, several underlying exposure-response functions may occur simultaneously during exposure, one for each mode of action. This further adds to the uncertainty in the selection of any exposure-response function.

Two areas of research are necessary to address these uncertainties, epidemiology studies and clinical studies. Additional epidemiology studies designed to investigate the relationship between the level of infestation and the prevalence of human health effects would be most useful in addressing the uncertainty. Since gypsy moth infestations occur during the spring when there are other agents, such as pollen and other insects, that may cause similar health effects, the proper selection of control populations (that is, populations not exposed to the gypsy moth) is essential. Furthermore, these studies would be useful for characterizing the exposure-response relationship and selecting an exposure-response model. Clinical studies

would help to define the nature of the adverse response, toxic or immunological, and the prevalence of sensitive individuals in the general population.

3.5.2. Workers and the General Public

The risk characterization for workers and the general public is summarized in Table 3-2. The ranges of risk for the general public are based on the ranges of exposure given in column 2 of this table.

For the general public, risks are characterized for four exposure scenarios with egg-mass densities ranging from 50 to 20,000 egg masses/acre. This categorization is somewhat judgmental. Egg masses of 100/acre or less are usually observed in infested areas on the east coast (Reardon and others 1993). Egg mass densities of 20,000 egg masses/acre are uncommon and are likely to occur only in localized areas during gypsy moth outbreaks.

The estimate for workers and other exposed individuals is intended to represent the proportion of individuals that would have adverse health effects after a sufficiently high level of exposure. These values are highly subjective. The estimate of 25% is in the range of the most commonly reported frequencies of responses for groups of individuals who developed skin lesions after confirmed contact with the gypsy moth. The lower rate of 10% approximates the proportion of individuals that had no known contact with the gypsy moth before contact in a clinical study but had skin reactions after challenge. The upper range of 100% is based on the assumption that all individuals may be sensitized to the gypsy moth after prolonged or repeated exposures or that at least one component of the response is toxic rather than allergenic. In either case, all individuals would be expected to respond with sufficiently severe exposures.

3.5.3. Cumulative Effects

Two types of cumulative effects may be considered in assessing the consequences of exposure to the gypsy moth. During an infestation, repeated exposures will occur in the population for the duration over which exposure to the gypsy moth instars occurs. In addition, cumulative effects may be induced from year to year as infestations reoccur. Cumulative effects from exposure to the larvae during a single season are essentially encompassed by the epidemiology study on which the risk assessment is based (Tuthill and others 1984) because this study monitored effects in populations during the period in which early instars were present. The available data do not permit a definitive assessment of the cumulative effects of exposure to the gypsy moth over several seasons. As discussed in the hazard identification (see section 3.2), there is evidence to suggest that one of the mechanisms involved in the dermal effects associated with exposure to the gypsy moth involves an allergic reaction. Thus, it is plausible that some individuals may become sensitized to the gypsy moth after repeated exposures over one or more seasons.

3.5.4. Connected Actions

There is no evidence to assess the consequences of connected actions involving the various program activities or other common activities. As detailed in section 5, Gypchek contains gypsy moth parts and may cause irritant effects similar to those caused by the gypsy moth. Consequently, it might be speculated that exposure to both gypsy moth larvae and Gypchek could be additive.

3.5.5. Groups at Special Risk

Young children are a group at special risk. This finding is clearly demonstrated in the study by Tuthill and others (1984) and suggested by the studies on school children affected by gypsy moth infestations (Aber and others 1982, Anderson and Furniss 1983). Most likely, this sensitivity is the result of higher exposures because children, compared with adults, spend more time outdoors.

4. Bacillus thuringiensis var. kurstaki (B.t.k.)

4.1. Program Description

Bacillus thuringiensis (B.t.) are rod-shaped, gram-positive, spore-forming aerobic bacteria found in most of the world. The vegetative cells are 1 μm wide, 5 μm long, and have flagellae, which are short hair-like structures used for locomotion. B.t. is ubiquitous in the environment and can be isolated from soil, foliage, water, and air (Martin 1994).

B.t. was first isolated from diseased silk worms in Japan in 1901. In 1915, Berliner isolated B.t. from diseased flour moths. There are 22 known varieties and 800 strain isolates of B.t. The insecticidal potency of B.t. varies among insects, depending on the strain and the variety of bacteria (Frankenhuyzen and others 1992, Navon 1993).

B.t. var. kurstaki (B.t.k.) was first isolated in France by Kurstak in 1962. A new strain of B.t.k. was identified in the pink bollworm and named the HD-1 strain by Dulmage and others (1971). All commercial formulations of B.t.k., summarized in Table 4-1, use the HD-1 strain (U.S. Department of Agriculture, Forest Service 1994a). More than 1 million pounds of B.t.k. are applied annually in the United States to control the gypsy moth (Green and others 1990). Although B.t.k. formulations may be applied by aerial spray (U.S. Department of Agriculture, Forest Service 1991) or by ground spray, the number of aerial applications far exceeds the number of ground applications. In the APHIS database on gypsy moth eradication efforts, records dating from 1980 to the present indicate that B.t.k. was applied to 643,804 acres by aerial spray and to only 1,480 acres by ground spray. Between 1980 and 1994, approximately 5.3 million acres were treated with B.t.k. formulations to suppress gypsy moth populations in the eastern United States (U.S. Department of Agriculture, Forest Service 1994a).

The potency of commercial formulations of B.t.k. is expressed as BIU/gallon (Table 4-1). The term "BIU" is an acronym for billions of international units. This potency is measured in a bioassay using the cabbage looper (Dulmage and others 1971). During production, each commercial batch of B.t.k. is used in the bioassay to determine the LC_{50} for the test insect, expressed as mg product/kg diet. The potency of the batch is then adjusted to the nominal requirement, as specified for the various formulations in Table 4-1. Hence, the use of BIU/acre to express an application rate is meaningful in terms of insecticidal efficacy, assuming that toxic potency to the gypsy moth is related to the toxic potency to the test species used in the bioassay of the commercial product.

B.t.k. vegetative cells produce spores and crystals. The crystals are repeating protein subunits composed of proteinaceous toxins, enzymes, and other proteins. B.t.k. must be eaten in order to be effective as an insecticide. The crystals dissolve in insect gastrointestinal tracts that have a high pH (that is, they are alkaline or basic). Proteolytic enzymes in the insect gut and in the crystals themselves break down the crystals (prototoxins) into active

toxic subunits. The toxins attach to the lining of the mid-gut of the insect and rupture the cell walls, which allows the alkaline contents of the gut to spill into the body cavity (Drobniewski 1994). The B.t.k. spores germinating in the intestinal tract enter the body cavity, through the perforations made by the crystal toxins, and replicate, causing septicemia. The body tissues of the insect are consumed by B.t.k. The infected insect usually stops feeding within 1 hour (Abbott Labs 1992).

Some strains of B.t. contain the beta-exotoxin, which is mutagenic in mammals (Meretoja and others 1977). Such strains are not permitted in Canada or the United States (British Columbia Ministry of Health 1992, U.S. EPA 1988b). B.t.k. does not contain the beta-exotoxin.

4.2. Hazard Identification

Reviews regarding the regulation of insecticidal agents suggest that there is a low level of concern about human exposure to B.t.k. For example, in its review of technical information submitted by manufacturers of B.t.k. formulations, U.S. EPA (1986b) concluded that B.t. is not a human pathogen but can cause irritation or inflammation. Similarly, in a more recent review, the British Columbia Ministry of Health (1992) concluded that the available data indicate that B.t.k. is specific to lepidopteran larvae and does not pose a threat to humans.

With minor reservations, this risk assessment concurs with these evaluations. That is to say, under normal conditions, B.t.k. formulations do not pose a substantial risk to workers or the general public. In making this assessment, a clear distinction must be maintained between the microorganism B.t.k. and the commercial preparations of B.t.k. As with any preparation containing microorganisms, potential concerns include pathogenicity, persistence of the microbial agent in the human body, the genetic stability of the microbial agent in the environment, and the ability of the microbial agent to interact with other microorganisms. These concerns, as they relate to B.t.k. exposure, are discussed below. As a complex mixture of chemicals, B.t.k. formulations may have toxic properties that are unrelated to the presence of bacteria. For example, the available data regarding human exposure to B.t.k. formulations suggest that they cause eye, skin, and respiratory tract irritation. It is not clear, however, that these effects are caused by the microbial agents. This inability to identify clearly the agent or agents in B.t.k. formulations associated with various potential adverse human health effects complicates the risk assessment.

4.2.1. Commercial Formulations

B.t.k. formulations are complex chemical mixtures. Specific information regarding the components of these mixtures and the methods by which B.t.k. is cultured in commercial preparations is proprietary. A general discussion, however, is provided by Bernhard and Utz (1993). B.t.k. is cultured in large vats that contain, for the most part, water and nutrients.

The nutrients consist primarily of sugars, starches, proteins, or amino acids. These nutrients are not added as pure and defined compounds but rather as chemically complex and variable biological materials such as animal foodstuffs, a variety of flours, yeasts, and molasses. Relatively small quantities of essential elements, minerals, or salts also may be added to create optimal growth conditions. Adjuvants, such as antifoaming agents, may also be used at various stages of production to enhance growth or facilitate the recovery of B.t.k. from the growth media. The other components of the formulation are mostly water and a complex mixture of culture media and metabolites. The exact composition of these materials is similar but may vary among manufacturers. Moreover, the composition used by one manufacturer may change over time, as different sources of nutrient material are used.

The chemical and biological variability of B.t.k. formulations has not been be well characterized. One index of variability, however, is the number of viable spores in the formulation. Because the viable spores, together with the crystalline toxins, are agents that exert a toxic effect on the gypsy moth, there are some data regarding the number of spores in various formulations. For Foray 48B, microbial analyses of individual batches over a 2-year period indicate that the number of spores per unit of weight of the formulation can vary by a factor of 50 (Overholt 1994).

4.2.1.1. Contaminants

As with any preparation of bacteria, there is a potential for contamination with other possibly pathogenic microorganisms, which must be addressed by proper quality control procedures (Bernhard and Utz 1993). Between 1985 and 1987, random samples of B.t.k. purchased by the various states or provinces were found to contain various bacterial contaminants, although none were considered pathogenic. In response to the concerns raised by this contamination, manufacturers took steps in 1988 to ensure that each batch of B.t.k. is free of detectable levels of contaminants. Since 1988, no substantial levels of bacterial or yeast contaminants have been found in B.t.k. samples (Reardon and others 1994). As part of an epidemiology study conducted by Noble and others (1992), Foray 48B samples were tested and found to contain no other bacteria (section 4.2.3).

U.S. EPA (1988b) requires that spore preparations of B.t. are produced by pure culture fermentation procedures with adequate quality control measures to detect either contamination with other microorganisms or changes from the characteristics of the parent B.t. strain. In addition, prior to final formulation, each lot must be tested by subcutaneous injection of at least 1 million spores into at least five mice. Details of the quality control processes implemented by Novo Nordisk for its Foray products have been provided by Overholt (1994) for the preparation of this document. Each batch of Foray is tested and rejected if any levels of potentially hazardous bacteria (for example P. aeruginosa, Salmonella sp., or S. aureus) are detected. In addition, maximum levels have been established for coliform bacteria (10 cfu/g), streptococci (10,000 cfu/g), fungi (100 cfu/g), and yeast (100 cfu/g). These limits

have been reviewed and accepted by U.S. EPA (Overholt 1994). (See section 4.2.2 for a discussion of cfu as a unit of measure for microorganisms.)

4.2.1.2. Inerts

The significance of the inerts in the commercial formulations of B.t.k. to public health is a matter of concern to the general population. This concern is exacerbated because the identities and quantities of the inerts cannot be made public (Otvos and Vanderveen 1993). Novo Nordisk (1993) has prepared a brief summary of the issues associated with the use of inerts in Foray 48B and the proprietary nature of inerts. This document is useful because it contains some specific information that can be disclosed. Foray 48B is a mixture of B.t.k. and fermentation materials, which comprise almost 90% of the product. The added inerts (that is, those other than incidental fermentation products) include materials to inhibit the growth of bacterial or fungal contaminants. These additives are approved for use in foods in both the United States and Canada. All of the Novo Nordisk inerts are on U.S. EPA List 3 or 4 (see section 2.3). No volatile solvents are used in Foray 48B. All inerts have been reviewed by the U.S. EPA and by various agencies in Canada. Other than this Novo Nordisk (1993) summary, there is only one reference in the available literature regarding these inerts that can be cited. The Oregon Department of Human Resources has reviewed the complete formulation in Foray 48B and determined that "... exposure to the ingredients in the Foray 48B formulation are unlikely to pose a public health threat to populations exposed to the spray in eradication programs" (Fleming 1993 p.1).

Discussions regarding the inerts in other B.t.k. formulations were not located in the available literature. All of the inerts in the B.t.k. formulations produced by Abbott Laboratory are on U.S. EPA List 4. During the preparation of this risk assessment, U.S. EPA files on product chemistry were reviewed for all B.t.k. formulations. The individual components do not appear to be highly toxic agents. Nonetheless, some of the components are themselves complex mixtures of nutrients, which have not been fully characterized. Furthermore, the exact chemical nature of these nutrient mixtures is likely to vary over time.

A component-based assessment of each inert has not been conducted. That is because component-based assessments for highly complex mixtures generally are not useful, given that as the number of components in a mixture increases, the uncertainty of a component-based risk assessment also increases (Mumtaz and others 1994, U.S. EPA 1986a). As recommended by U.S. EPA (1986a), the risk assessment will be based on the mixtures of concern, in this case commercial formulations of B.t.k. The limitations and benefits of this approach are discussed further in the risk characterization (section 4.5).

4.2.2. Measures of Exposure

The complex and variable nature of the B.t.k. formulations used to control the gypsy moth imposes some severe limitations on the analysis of the available data and the consequent risk assessment. One such limitation is the selection of the most meaningful method of assessing human exposure to B.t.k. formulations. Although BIU per acre may be meaningful as an exposure metameter for the gypsy moth, it is not necessarily or even likely to be a meaningful measure of human exposure. Toxicity to sensitive insects such as the gypsy moth is generally attributed to a combination of the delta-endotoxin and the spore coat. These two factors probably account for the potency of the commercial formulations in the bioassays used to determine the BIU per mg of commercial product. Unlike the gut of the gypsy moth, which has a high pH (that is, the gut is alkaline or basic) the stomach of most mammals, including humans, has a low pH (that is, the stomach contents are acidic). Thus, the delta-endotoxin is not toxicologically significant for humans.

Another commonly used measure of exposure is colony forming units or cfu. When B.t.k. formulations are applied, either by aerial spray or ground spray, one or more viable spores contained in droplets or particulates is suspended in the air and deposited on sprayed surfaces. These droplets may be collected, either by air sampling or direct deposition, on to various types of filters. The filters are then cultured in a nutrient medium under conditions conducive to bacterial growth. As the bacteria grow, visible masses of bacteria, referred to as colonies, appear on the media. In the case of monitoring B.t.k. formulations, some of the colonies will be B.t.k. and some colonies will be other endogenous bacteria. Microscopic examination, differential culturing, or other methods may be used to determine the number of colonies that are B.t.k. By this general method, the number of cfu per unit of surface area or volume of air, depending on the sampling method, may be determined. Each cfu can be formed from a droplet or particulate that contains one or more viable spores. Thus, the number of cfu per unit of surface area or volume of air does not correspond directly to the number of viable spores per unit of surface area or volume of air. Dilution methods can be used to determine the number of viable spores (Palmgren and others 1986).

The significance of cfu as a measure of human exposure is limited. There is little indication that B.t.k. is a human pathogen. Consequently, the number of viable spores, albeit an important measure of exposure for the gypsy moth, is not toxicologically significant to humans. In this respect, cfu like BIU are of limited significance, even if the distinction between cfu and the number of viable spores is ignored. Nonetheless, at least for short-term exposures, cfu can be used as a practical measure of exposure to the B.t.k. formulation. For example, assume that an aerial application of a B.t.k. formulation is made and that two air samples are taken, one immediately at the spray site and one upwind from the spray site. Droplets containing viable spores as well as other components in the B.t.k. formulation are sampled at both sites for a fixed period of time. If the sample taken at the spray site yields 200 cfu and the sample upwind yields 20 cfu, it would be reasonable to conclude that the level of human exposure to the B.t.k. formulation at the upwind site is 10% of that directly

beneath the spray. This makes no assumptions, however, about what the toxic agent is or even if there is a toxic agent. In this case, the number of cfu is used as a surrogate for exposure to the formulation.

As detailed in the exposure assessment (section 4.3), data are available regarding cfu per volume of air for intervals up to several days after spraying. For such measurements, it is not reasonable to assume that cultured colonies represent exposure to the formulation. Some components in the formulation, such as water or other volatile materials, will have evaporated. Materials that are not volatile, such as starches, sugars, minerals, proteins, and amino acids, will have degraded or partitioned from the viable spores. Thus, measurements of cfu taken long after the spray application can be interpreted as viable B.t.k. spores that probably adsorbed to particulates and were re-suspended. There is no reason to believe that these spores are toxic to humans; therefore, these measurements have no clear toxicological significance.

Several of the available toxicity studies express exposure in units of mg of formulation per unit of body weight or volume of air, depending on the route of exposure. As with cfu, these measures may be applicable to the risk assessment in so far as the anticipated exposures involve the entire commercial formulation. Exposures of this nature usually will occur during or immediately after application.

4.2.3. Pathogenicity and Persistence

One of the principal concerns in the use of Bacillus species to control insects is the potential pathogenicity of the organism to nontarget species, including humans. Various Bacillus species, including some varieties of B.t., are clearly pathogenic to mammals (Drobniewski 1994). B.t.k. has been tested for pathogenicity and other toxic effects in a variety of experimental mammals and by several routes of exposure. The most relevant studies are summarized in Table 4-2. In these studies as well as others submitted to U.S. EPA as part of the registration process, there is no evidence of pathogenicity in experimental mammals (U.S. EPA 1986b and 1988b).

A distinction must be made between pathogenic activity and persistence. A pathogen will actively multiply in the host, and, in doing so, may cause damage. In this respect, B.t.k. is clearly pathogenic to some insects including the gypsy moth. Persistence refers to the ability of the organism to survive rather than multiply within a host. As summarized in Table 4-2, several studies indicate that B.t.k. can be recovered from exposed mammals but that recovery decreases relatively fast after exposure is terminated. In this respect, the study by Oshodi and Macnaughtan (1990) is somewhat unusual. After inhalation exposure to Foray 48B, the numbers of viable B.t.k. spores recovered from the lungs did not decrease substantially during a 28-day observation period.

There is only one published study purported as evidence that B.t.k. is pathogenic to humans. Samples and Buettner (1983) report that a farmer splashed a commercial formulation of B.t.k. (DiPel solution) in his right eye, causing eye irritation. Irrigation of the eye and application of an antibiotic ointment were ineffective in relieving the symptoms. Hence, 4 days after the accident, the farmer was treated with 0.1% ophthalmic solution of dexamethasone, a corticosteroid given to relieve the irritation. A corneal ulcer was observed 10 days after the accident. The farmer was then treated with subconjunctival injections of antibiotics. B.t.k. was isolated and cultured from the ulcer. The farmer recovered with no permanent eye damage. Although this incident might be interpreted as evidence of an eye infection with B.t.k., it can also be interpreted as severe eye irritation accompanied by the recovery of incidental, viable B.t.k. known to have been accidentally introduced into the farmer's eye (U.S. EPA 1986b).

The other available human data are reasonably consistent with the data on experimental mammals. B.t.k. does not appear to be pathogenic, although viable B.t.k. may be recovered from humans up to several months after exposure. This assessment is based primarily on two epidemiology studies, one of which was conducted in Oregon and another conducted in British Columbia. In 1985 and 1986, a gypsy moth aerial spray program was conducted in Lane County, Oregon. An exposure assessment for this program has been published by Elliott and others (1988). A somewhat more detailed summary of these data is presented in a NIOSH Health Hazard Evaluation Report (Elliott and others 1986). In addition, Green and others (1990) published the results of a health monitoring survey associated with the Oregon program. In 1992, Agriculture Canada and the British Columbia Ministry of Forests conducted a combined aerial and ground spray program in the Lower Mainland of British Columbia. An overview of an epidemiology study of this program has been presented by Noble and others (1992), and details of the monitoring of ground workers in this application have been provided by Cook (1994). Clarification of additional aspects of the epidemiology studies has been provided by Noble (1994).

In the Oregon program, spray operations were conducted in April, May, and June of 1985 and 1986. B.t.k. was applied to more than 250,000 acres in 1985 and 270,000 acres in 1986. The B.t.k. was sprayed from helicopters in three separate applications (approximately 7–10 days apart) over forest, rural, and urban areas. All spraying was conducted between daybreak and approximately 10:00 a.m. (Elliott and others 1988). None of the publications on the Oregon Program report the nominal application rate. According to the Oregon Department of Agriculture (Hillborn 1994), the application rate was 16 BIU/acre of a Dipel formulation.

The health surveillance activities that accompanied the Oregon spray program are reported by Green and others (1990). The total population of Lane County at the time of the study was 260,000. The 1985 spray covered an area with a population of approximately 80,000; the 1986 spray covered an area with a population of approximately 40,000. A surveillance program was established involving the four largest clinical laboratories in the area, three of which were associated with hospitals and one of which was an outpatient facility. All

clinical cultures that were positive for any Bacillus species were subcultured, and the presence of B.t.k. in the subcultures was determined. As a control, the same procedure was followed for an unsprayed community approximately 60 miles from the spray area. No B.t.k. positive samples were identified from the unsprayed community. In the samples from Lane County, a total of 55 B.t.k. positive cultures were found over the 2-year study period, 52 of which were associated with incidental contamination. Two of the three remaining samples may have been the result of contamination. The third sample was from an abscess in an IV drug user and "..., there was some evidence that the positive cultures resulted from contamination, but it could not be conclusively determined whether B.t. was a contaminate of the culture or the cause of illness." (Green and others 1990 p. 849).

Noble and others (1992) conducted an epidemiology study on residents of British Columbia during a Foray 48B spray that involved a period of approximately 10 weeks, April 18 to June 30, 1992. Although not specified in the study, the aerial application rate was 50 BIU/ha or 20.2 BIU/acre (50 BIU/hectare ÷ 2.471 acres/hectare) (Bell 1994b).

According to records kept by a selected group of family practice physicians, there were no detectable effects of exposure among members of the general public (Noble and others 1992). The records of 1,140 physicians' office visits were reviewed. Of these, 675 were classified as clearly unrelated to symptoms that might be associated with the spraying. The remaining records involved reports of allergies, asthma, rhinitis, conjunctivitis, infections of the ear, sinus, or respiratory tract, and skin rashes. Although the available data did not permit an assessment of each individual's exposure to B.t.k., available information on postal zones for each individual's residence suggested that the numbers of these complaints were evenly divided between individuals living inside and outside of the spray area. In addition, 3,500 records of admissions to hospital emergency departments were reviewed. In no case was B.t.k. implicated as an agent causing any disease or clinical complaint.

An analysis of all Bacillus isolates from all the hospitals and laboratories in the study area indicated that many people were exposed to B.t.k.; however, in all cases, chromatography of cellular fatty acids indicated that the B.t.k. recovered from these sources was different from that used in the aerial spray (Noble 1994). Of 10 different vegetable samples assayed for B.t.k., five were positive during the spray period. As with the B.t.k. recovered from human samples, the B.t.k. in the vegetable samples was different from the B.t.k. used in the aerial spray. This indicates that oral exposure to B.t.k. was common in this area but that this exposure was not attributable to the aerial spraying. As discussed in the program description (see section 4.1), B.t.k. is commonly found in nature, and widespread incidental exposure to B.t.k. is to be expected.

In no case was B.t.k. the agent causing an infection (Noble and others 1992). When B.t.k. was recovered in stool samples, the medical histories did not suggest that the B.t.k. was associated with signs or symptoms of food poisoning or a disease with watery diarrhea similar to or suggestive of Bacillus cereus.

Some ground workers from the British Columbia study involved in the application of B.t.k. remained culture positive for long periods of time (Cook 1994). Of 115 workers exposed to B.t.k. and available for follow-up studies, 15 yielded positive B.t.k. cultures from nose swabs 30–60 days after exposure. Five were positive at 120 days after exposure. No positive cultures were identified after 140 days from the termination of exposure. Signs of respiratory or nasal infections and other health effects attributed to B.t.k. were not observed in any of the workers at any time.

Other epidemiology reports involving exposure to B.t.k. are much less detailed, but they generally support those described above. In a study in which B.t.k. 3a3b was applied at a rate of $22 \cdot 10^6$ to $25 \cdot 10^6$ IU/hectare to control the spruce budworm, no medical problems were detected in a survey conducted among B.t.k. workers, 80 volunteers living in the treated area, and 80 controls living in an untreated area (Valero and Letarte 1989). Only a few workers seemed to develop antibodies to B.t.k.; however, in studies such as these, unspecified reactions due to antibody formation in response to other Bacilli cannot be ruled out (British Columbia Ministry of Health 1992). Industrial reports indicate that B.t.k. can be cultured from various superficial sites on exposed humans and that antibodies to B.t.k. are greater in individuals in areas sprayed with B.t.k. than in individuals in untreated areas (Abbott Labs 1992). No illnesses or infections attributed to B.t.k. were noted. The medical records of workers exposed to B.t.k. contained no references to ocular infection, soft tissue infection, or chronic respiratory infection attributable to B.t.k. (Abbott Labs 1992).

4.2.4. Environmental Persistence and Stability

A large body of literature indicates that B.t.k. does not persist for long in the environment (Otvos and Vanderveen 1993). The persistence of B.t.k. and the toxin on foliage is short unless special formulations are used to protect the B.t.k. and the toxin from degradation (by ultraviolet light) or removal (by rainfall). B.t.k. does not seem to replicate or to accumulate in gypsy moth predators (Burges 1982).

B.t.k. loses about 50% of its insecticidal activity within 1–3 days (British Columbia Ministry of Health 1992). Sunlight inactivated 50% of B.t.k. spores within 30 minutes and 80% within 60 minutes (Krieg 1975). Spores adhering to the exposed upper surfaces of leaves may be effective for only 1 or 2 days; spores deposited on the undersurface may be effective for 7–10 days. The inactivation of both spores and crystals may be due to the production of peroxide or peroxide radicals after ultraviolet irradiation of the amino acids. Moist, unprotected spores are killed rapidly by exposure to sunlight (Cantwell and Franklin 1966) but are less susceptible under very dry conditions (Pinnock and others 1971).

B.t.k. can survive as spores in most types of soils, but will not grow at pH < 5.2 (Saleh and others 1970). B.t.k. does not seem to accumulate in soils, despite repeated applications (Aizawa and Ohba 1985). The fate of B.t.k. in soil depends somewhat on microbial competition (Akiba and others 1977). Spores may remain active in soil for at least 4 months, especially in the absence of germination-inducing stimuli (Jaques 1973). The varietal status

of B.t.k. is stable in soil as indicated by the absence of cross-contamination when two serotypes were sprayed in close proximity (DeLucca and others 1981). This also suggests that B.t.k. does not migrate in soils. In another study, 24% of the endospores remained viable in soil after 135 days, while pathogenicity was <1%, suggesting that the delta-endotoxin decays far more rapidly than the spores (Pruett and others 1980).

Field studies indicate that B.t.k. may persist for several months in water. In Nova Scotia, during operational spray programs, B.t.k. spores remained viable (about 50%) in fresh lake water for at least 70 days (Menon and deMestral 1985). In seawater, less than 10% survived after 90 days.

The exchange of genetic material between B.t.k. and other bacilli (for example, B. subtilis and B. cereus) has been demonstrated in the laboratory (Meadows 1993). Isolates of B. cereus have been identified as etiological agents causing mammalian infections and/or human food poisoning. The formation of B.t.k. delta-endotoxin is plasmid coded, and B.t.k. delta-endotoxin coding plasmids can be transferred into strains of B. cereus with formation of delta-endotoxin crystals in the B. cereus recipients. These crystals have the same antigenic properties as crystals from the B.t.k. donor; however, the possibility of B.t.k. acquiring food poisoning capabilities from B. cereus or the possibility of B. cereus toxins to be present in commercial B.t.k. preparations is remote (British Columbia Ministry of Health 1992, Otvos and Vanderveen 1993, U.S. EPA 1986b)

4.2.5. Irritant Effects

All human exposure to B.t.k. is likely to involve a combination of dermal and inhalation exposure, with the potential for some incidental oral exposure. Dermal and inhalation exposure may pose some risk to workers and the general public. As summarized in Table 4-2, commercial formulations of B.t.k. have caused eye, skin, and respiratory irritation in experimental mammals. Similar effects were observed in the epidemiology study of ground workers exposed to B.t.k. (Cook 1994). During the ground application, the commercial formulation of B.t.k., diluted with water, was delivered as a high pressure spray from high-lift units. Dilutions ranged from an initial 200:1 to 75:1. The decrease in the dilution rate was associated with the use of a finer spray. In the last spray cycle, a jet turbine aerosol generator (Rotomister) mounted on a trailer was used. Two contractor teams, designated **A** and **B**, were involved in the ground applications. A separate group of workers was involved in monitoring the effectiveness of the aerial application by the placement of cards used to measure droplet deposition. These individuals were generally exposed to air-delivered aerosol during the aerial application and for 2 hours or more after the application. In general, the workers did not wear protective equipment (for example, goggles or face masks).

Worker exposure was monitored by microbiological air sampling. Nucleopore polycarbonate filters sealed in plastic filter cassettes were connected to dual high volume constant flow

portable air pumps. These were attached in the individual breathing zone of each worker. Pump volume and exposure time were recorded for each worker. The filters were assayed using quantitative dilution methods (Palmgren and others 1986).

As indicated in Table 4-3, mean exposures for the different job groups ranged from 0.3 million cfu/m^3 (card handlers in the aerial applications) to 5.9 million cfu/m^3 (sprayers). When data were categorized according to three exposure groups based on total cumulative exposure (0–100, 101–200, and >300 million cfu), there was a positive association between exposure and the number of symptoms per person. This association is illustrated in Figure 1 and summarized in Table 4-4. The highest reported cumulative exposure was 720 million cfu (sprayers); the lowest exposure was 5.4 million cfu (card handlers). Levels of B.t.k. exposure in the control population were assumed to be negligible. A comparison of the symptoms reported in the control and exposed groups is presented in Table 4-5. In this table, all ground spray workers are combined rather than grouped by exposure category. Symptoms, including transient irritation of the eyes, nose, and throat, dry skin, and chapped lips, developed in approximately 63% of the workers, but in only 38% of the control group. No days of work loss were attributable to B.t.k. exposure.

4.2.6. Effects on Eyes

In addition to animal studies indicating that commercial B.t.k. formulations cause eye irritation (see Table 4-2), the literature contains two reports of eye irritation in humans after exposure to B.t.k. (Green and others 1990, Samples and Buettner 1983). The study by Samples and Buettner (1983) regarding the pathogenicity and persistence of B.t.k. is discussed in detail in section 4.2.3. The other study describes an incident in which a worker involved in the application of B.t.k. splashed the B.t.k. mixture in his face and eyes. The worker developed dermatitis, pruritus, burning, swelling, and erythema, with conjunctival irritation. A culture of the conjunctiva was positive for B.t.k. The worker was treated effectively with steroid cream applications to the eyelid and skin.

Ocular exposure to B.t.k. does not always result in serious eye irritation. Nobel (1994) briefly summarizes an incident in which two individuals on bicycles were accidently sprayed in the face by ground spray workers. The face and eyes were washed immediately after the incident, and no residual eye irritation developed in either individual over a 21-day follow-up period. In a separate incident, two workers on the ground spray team in the British Columbia study were accidently sprayed in the face with the B.t.k. formulation. These workers experienced only slight redness of the eyes for several hours after exposure (Cook 1994). As summarized in Table 4-5, the ground spray workers in this study reported a higher rate of eye irritation, compared with the control population (Cook 1994).

4.2.7. Other Effects

Most of the studies summarized in Table 4-2 are reasonably consistent with the general assessment regarding the toxicology of B.t.k. formulations: irritant effects but no systemic toxic effects or infectivity. Two studies, however, are inconsistent with the other available information. In one of these studies, inhalation exposure of rats to very high levels of B.t.k. caused piloerection (an atypical condition in which the hair stands erect), lethargy, and frequent urination during exposure (Holbert 1991). Alopecia (hair loss) was observed in the rats several days after exposure. This study involved whole body exposures over a 4-hour period to a level of B.t.k. formulation (3.22 mg/L Foray 76B) that caused the rats to become coated with the test material. The investigators indicated that the hair loss was probably related to B.t.k. exposure. While the implications for human risk assessment, if any, are unclear, this is an unusual finding. The reason for the hair loss cannot be determined, and this effect is inconsistent with other studies on B.t.k.

Another unusual finding is reported by Berg (1990). In this study, rats were given an intravenous dose of 1 mL Foray 48B. Histopathological findings in the liver and the reticuloendothelial system were attributed to a background infection (see Table 4-2). The pathology results, however, were more severe in the exposed group compared to the controls, suggesting that the B.t.k. aggravated this disease condition. Again, given the route of exposure and very high dose used, this study may have no direct implication for human health risk assessment. Nonetheless, this is an unusual finding that is not consistent with the other available information on B.t.k.

4.3. Exposure Assessment

The methods of applying B.t.k. suggest that the likeliest routes of exposure for the general public are oral, dermal, and inhalation. In addition to these routes of exposure, accidental parenteral or ocular exposures may occur in workers. The best available monitoring data for assessing worker and general public exposure to B.t.k. from aerial sprays are reported in the Oregon study (Elliott and others 1986, 1988). These data are from urban areas and cannot be used for making canopy-specific exposure assessments. A heavy canopy of vegetation is likely to reduce the amount of exposure. Hence, an exposure assessment based on these data is likely to be conservative for areas that have a heavy canopy of vegetation.

In the Oregon study, portable sampling pumps with 37-mm (0.8 micron pore size) cellulose ester membrane filters were used for personal and area air monitoring. Flow rates on the sampling pumps ranged from 0.1 to 2.0 L/minute, and the duration of sampling ranged from 0.25 to 4 hours. All personal monitoring done during 1986 was conducted with a flow rate of 0.1 L/minute. Microbial culture and microscopic examinations were used to assay for B.t. on the filter media. Initially, all plates (inoculated with membrane filters from the monitoring pumps) were incubated and inverted for 24 hours at 30°C, after which time colonies were counted. The plates were then incubated for 5 more days at room

temperature. Colonies resembling B.t. were examined microscopically. B.t. was identified by the presence of diamond-shaped toxin crystals (Elliott and others 1988). Measurements made during 1985 could not be expressed as cfu/m^3 because of the extreme numbers of colonies obtained on the culture plates. The results of the 1986 personal and area monitoring tests (expressed as cfu/m^3) are summarized in Tables 4-6 and 4-7.

Table 4-6 provides estimated exposure levels for aerial applicators based on data from Elliott and others (1986). B.t.k. concentrations in air were not substantially different for the pilots, the aerial observers, the safety officer, or the security guard. Concentrations ranged from 0 to 3,600 cfu/m^3, with a mean value of approximately 1,400 cfu/m^3. The lowest positive value was 800 cfu/m^3. The card checkers monitored by Elliott and others (1988) are in the general range of other aerial applicators, except for the worker who was in direct contact with the spray during card retrieval. The air concentrations for the card checkers was 0–5,600 cfu/m^3, with a mean of approximately 900 cfu/m^3, including zero values. The card checker in direct contact with the spray was exposed to 11,000 cfu/m^3.

The card handlers in the British Columbia study (Cook 1994), who seem to correspond to the card checkers (Elliott and others 1988), were exposed to about a 50-fold higher level of B.t.k. assayed as cfu/m^3, with a mean value of 300,000 cfu/m^3 and a range of 200,000–600,000 cfu/m^3 (Table 4-3). The substantial difference in exposure concentrations may be related to work practices. Elliott and others (1988) suggest that the card checkers avoided direct contact with the spray, emphasizing one worker's "brief direct contact." In contrast, Cook (1994) reports that the six individuals responsible for the cards were generally exposed to air-delivered aerosol during the fly over and for the 2 or more hours it took to collect the cards. More importantly, however, the Oregon and British Columbia studies used different analytical methods to determine cfu, and different batches of B.t.k. formulations were used in these two applications. As discussed in section 4.2.2 on measures of exposure, the levels of viable spores in B.t.k. formulations from the same manufacturer may vary by a factor of at least 50. Thus, the levels of exposure in these two studies are not suitable for direct comparison.

As indicated in Table 4-3, ground workers spraying B.t.k. may be exposed to very high levels of the agent, with air concentrations ranging from 0.2 to 15.8 million cfu/m^3 (Cook 1994). The maximum cumulative exposure for these workers was 720 million cfu, and lowest cumulative exposure for these workers was 5.4 million cfu. The applicability of these values to the occupational exposure of other ground workers is questionable. Actual exposures depend on the concentration of B.t.k. in the applied solution, the specific application methods, the duration of exposure, and the job category.

4.4. Dose-Response Assessment

4.4.1. Workers

Suspended B.t.k. with secondary dermal contact is the exposure scenario of primary concern. This is the likeliest exposure scenario for ground workers. Data from the British Columbia study in workers (Cook 1994) is the only study from which a dose-response assessment can be made for this scenario.

Cook (1994) characterizes a positive dose-response relationship for ground workers (Figure 4-1). The nature of the response can be characterized as irritation to the skin, eyes, and respiratory tract, as detailed in Table 4-5. The dose or cumulative exposure in cfu can be characterized in greater detail based on the information provided by Cook (1994). Low level exposure ranged from 5.4 million cfu, the lowest cumulative exposure reported, to 100 million cfu. High level exposure ranged from greater than 300 million cfu to 720 million cfu, the highest reported cumulative exposure.

In the low exposure group (5.4–100 million cfu), the reported response is 1.5 symptoms/person, including all symptoms, not just those attributed to B.t.k. exposure (Figure 4-1). This is about twice the response for the control group (0.8 symptoms/person). Consequently, 5.4–100 million cfu may be regarded as a LOAEL. Using the geometric mean of the range for the low exposure group (about 20 million cfu) and dividing by a factor of 10 to go from a LOAEL to a NOAEL as well as an additional uncertainty factor of 10 for sensitive individuals, the RRV for workers can be taken as 0.2 million cfu.

The endpoints covered by this dose-response assessment are of minor clinical significance. As noted by Cook (1994), there was no increase in the number of workdays lost for ground workers, compared to individuals in the control group.

As discussed in the hazard identification (see section 4.2), this dose-response assessment is specific to monitoring data from the British Columbia study because the cfu from one study may not be directly analogous to the cfu from other studies. As discussed in the risk characterization (section 4.5), this imposes substantial limitations on the characterization of risk.

No dose-response relationship can be proposed for aerial workers. As indicated in the monitoring studies done in Oregon (Elliott and others 1986, 1988), aerial workers are exposed to levels of B.t.k. that are slightly higher than the levels to which the general public is exposed.

4.4.2. General Public

As discussed in the hazard identification (see section 4.2), two detailed epidemiology studies, one conducted in Oregon (Green and other 1990) and the other conducted in British Columbia (Noble and others 1992) are available on populations exposed to B.t.k. formulations. Neither study detected any adverse effects in the populations exposed to B.t.k. sprays. The Oregon study involved the aerial application of Dipel at a rate of 16 BIU/acre over approximately 0.25 million acres with a population of about 40,000. This study focussed on the potential pathogenicity of B.t.k. The British Columbia study involved the aerial application of Foray 48B at a rate of approximately 20 BIU/acre. As in the Oregon study, no evidence of pathogenicity was detected. In addition, a surveillance program of a group of family physicians noted no substantial difference in the reports of symptoms that might be associated with B.t.k. exposure within and outside the spray areas.

Both of these studies may be regarded as NOELs, since neither detected any adverse effects in exposed populations. Since both studies covered large numbers of individuals in the general population, the need for any uncertainty factor is questionable. As discussed in the risk characterization (section 4.5), some individuals may be very sensitive to some components in these sprays. These individuals are likely to be considered part of a sensitive subgroup and might not be encompassed by the standard uncertainty factor of 10 for sensitive individuals, as discussed in section 2.3 (hazard identification, general methods). Because of the relatively large numbers of individuals involved in these studies, the highest NOEL, 20 BIU/acre is taken directly as the RRV for the general public. As discussed more fully in the following section, the use or omission of the uncertainty factor for sensitive individuals in the general population is a relatively minor source of uncertainty in the dose-response assessment. A far more important factor is that there is no positive hazard identification for members of the general public. This is to say that based both on the available epidemiology studies as well as the long history of use, there is no evidence that B.t.k. formulations cause adverse effects in the general population.

4.5. Risk Characterization

Since commercial formulations of B.t.k. are applied by aerial sprays and ground sprays in populated areas, this risk assessment is concerned with worker exposure and general public exposure to the insecticide. There is a large and compelling body of human experience as well as many toxicity studies on experimental mammals indicating that neither B.t.k. nor commercial formulations of B.t.k. are highly toxic or infectious.

For exposures of aerial application crews and the general public to B.t.k. during aerial application, the hazard identification is essentially negative. This is to say, that no adverse effects can be attributed to B.t.k. exposures.

Nonetheless, commercial formulations of B.t.k. are biologically active. Dose-response relationships for transient and relatively minor effects on the skin, nasal passages, and respiratory tracts of ground applicators have been demonstrated (Cook 1994). This study can be used directly to estimate risk for ground workers. Exposure during ground application to high levels of commercial formulations of B.t.k. is likely to cause transient dermal and respiratory tract effects in ground workers.

B.t.k. formulations may present other exposure risks. Most studies indicate that B.t.k. is not a pathogen and is eliminated relatively quickly by humans and experimental mammals. While the potential pathogenicity of B.t.k. does not seem to be of substantial concern, some studies suggest that B.t.k. may persist in mammals for a long time. Although most studies suggest that this persistence is of minor toxicological significance, a recent animal study indicates that intravenous exposure to a high level of B.t.k. might have exacerbated a preexisting infection (Berg 1990). In another recent study, short-term inhalation exposure to an extremely high level of a B.t.k. formulation caused hair loss (Holbert 1991). Although these reports may not have a direct impact on the assessment of human health risks associated with the common use of B.t.k., they are inconsistent with the majority of toxicological data on B.t.k. formulations and suggest that the biological effects of the formulations may not be well characterized or fully understood.

4.5.1. Uncertainties

For the general public, the greatest uncertainty involves the hazard identification. Based on the available data, it is not clear that any effects will be induced in the general public during normal aerial applications. The nature of this uncertainty is debatable. At one extreme, it may be argued that the available epidemiology studies were not designed to detect all types of effects in individuals who may be very sensitive to B.t.k. formulations. This position is based largely on conjecture and might be made regardless of improvements in the available information. At the other extreme, it could be argued that available information supports the assertion that B.t.k. presents no risks to the general public because no positive hazard identification can be made. This position ignores limitations in the available data. As discussed below, this risk assessment takes an intermediate position.

Other major uncertainties inherent in this risk assessment are due to the complex and variable nature of B.t.k. and B.t.k. formulations. These uncertainties are complex and interrelated:

The materials in B.t.k. formulations have not been fully characterized.

The composition of B.t.k. formulations may vary among and within manufacturers.

The toxic agent or agents of concern for human health assessment have not been identified.

The dose-response assessment for ground workers is based on only one formulation of B.t.k.

The most meaningful measure of human exposure to B.t.k. formulations cannot be determined.

The available data indicate that B.t.k. is probably not the toxic agent or at least not the only toxic agent in the commercial formulations used to control the gypsy moth. B.t.k. has been tested extensively in animals. In addition, several epidemiology studies have been conducted on human populations exposed to B.t.k. The weight of evidence indicates that B.t.k. is not pathogenic. Some of the effects caused by exposure to B.t.k. formulations might be attributed to B.t.k.; however, they might be attributed with equal or greater plausibility to the other biological or chemical components in the formulations or to other characteristics of the formulations.

BIU or cfu are of limited relevance in assessing human health effects. B.t.k. formulations do not partition instantaneously in the environment. That is, immediately after application, the mixture on the vegetation or in the air will be identical or very similar to the mixture released from the ground spray equipment or the airplane. During this period, cfu may be a reasonable measure of exposure to the total mixture, including the materials relevant to the assessment of human health effects. As time passes, however, the components in the mixtures will separate from one another, being transported or degraded at different rates. Although cfu remain a valid index of the number of viable B.t.k. spores or vegetative cells, they will no longer reflect levels of other materials in the original B.t.k. formulation.

A related uncertainty involves the comparison of different studies. The application of B.t.k. formulations is designed to achieve a desired coverage in terms of BIU per acre, but monitoring data are usually expressed as cfu per acre or cfu per m^3. For two different applications using different batches of B.t.k. formulation, the same application rate in BIU per acre may result in notably different levels of cfu per acre or cfu per m^3 because the number of cfu per unit weight of the formulation may vary substantially. Consequently, studies reporting effects or lack of effects associated with exposures expressed as cfu per acre or cfu per m^3 cannot be compared easily or directly. This leads to a major uncertainty in the current risk assessment. The rather detailed data on general public exposure to B.t.k. included in the Oregon study (Elliott and others 1986) cannot be used directly with the dose-response analysis from the British Columbia study involving worker exposure to B.t.k. (Cook 1994).

Although the results of this risk characterization are consistent with other epidemiology data, the dose-response assessment for ground workers is based on one study using one batch of one B.t.k. formulation, Foray 48B. That the same dose-effect relationship would be observed with different B.t.k. formulations or different batches of the same B.t.k. formulation is uncertain. As discussed in the hazard identification (see section 4.2), B.t.k. formulations are complex mixtures. Following the general guidelines in U.S. EPA (1986a),

the risk assessment is based on the complex mixture instead of the components of the mixture because of the complexity of the mixture and because no single component or small number of components in the mixture can be identified as the toxic agent. This mixture-based approach becomes less defensible as the components in the complex mixture vary among sources or over time. The concept of sufficient similarity, whether or not the data on one or more samples of a complex and variable mixture can or should be used for dose-response assessments for all such mixtures is discussed in U.S. EPA (1986a), but no definitive guidelines for addressing this question are provided.

The operational assumption of this risk assessment is that different batches or formulations of B.t.k. are sufficiently similar. This assumption is made because all formulations contain the same general kinds of materials, as discussed in section 4.2.1 on commercial formulations. Data regarding the specific components in each formulation do not suggest that the toxicities of these different formulations or different batches of these formulations are likely to be substantially different. Furthermore, the general agreement between the human and animal studies regarding the toxicity of B.t.k. supports the assumption of sufficient similarity.

The assumption of sufficient similarity may be challenged because of the substantial variability among batches of B.t.k. It may be argued, however, that the components known to vary cannot be clearly related to potential human health effects. Another argument against sufficient similarity may involve the reports of anomalous findings, including prolonged persistence, hair loss, and exacerbation of a disease condition. This argument remains a source of uncertainty that requires additional research to provide a better explanation of these unusual experimental results.

An additional source of uncertainty is the use of cumulative cfu per person as the measure of exposure. Many irritant and other toxic effects have threshold levels (that is, exposure levels below which no effects will be noted regardless of the duration of exposure). The use of cumulative cfu per person is based on a very different and contrary assumption: exposures in which the product of cfu per unit time and duration of exposure are equal will have an equal biological effect. In toxicology, this is referred to as Haber's law, which generally applies only to certain classes of agents and effects (Amdur 1980). The application of Haber's law to irritant effects is questionable. Thus, the use of cumulative cfu may be conservative because no thresholds are assumed, and, for irritant effects, thresholds are likely. This uncertainty may be compounded if monitoring data on cfu from periods long after application are used either in the exposure assessment or the dose-response assessment because the irritant agents may not be related to B.t.k. spores or vegetative cells.

There are several ways of addressing these uncertainties. Additional information, similar to that from the British Columbia study, may help to measure the variability of different B.t.k. formulations, among manufacturers and batches, and might be useful for evaluating dose-response models. More detailed analyses of the composition and variability of B.t.k. formulations would be useful in determining the agents responsible for the irritant effects of B.t.k. Such analyses might also explain some of the anomalous or poorly understood data

regarding the biological activity of B.t.k. formulations and help to identify other hazards or determine that other hazards are unlikely.

4.5.2. Workers and the General Public

The risk characterization for workers and the general public is summarized in Table 4-8. Exposure to B.t.k. is likely to cause irritation of the skin and respiratory tract in ground workers. Ground spray workers will be exposed to much higher levels of B.t.k. than aerial workers or the general public. Consequently, these effects are less likely to be observed in aerial workers or members of the general public after exposure to B.t.k. In all cases, the effects considered in this risk characterization are relatively mild and transient.

4.5.2.1. Ground Workers

As summarized in the dose-response assessment (see section 4.4), the relationship of exposure in cumulative cfu to general irritation of the eyes, skin, and respiratory tract is based on the responses of ground spray workers in the Cook (1994) study. The most direct approach to characterizing risk for workers is to take the exposure estimates for ground spray workers presented by Cook (1994). Thus, three exposure groups are used (low, medium, and high) taking the range of exposure for each group (Table 4-8). Since the exposure assessment and dose-response assessment are taken from the same study, the interpretation is identical to the results reported by Cook (1994). That is, ground spray workers are likely to be exposed to B.t.k. formulations at concentrations high enough to cause transient and relatively mild effects. The levels of response will be directly related to the levels of exposure and sufficiently higher than control rates to be readily detectable in an epidemiology study.

The most notable and potentially confusing components of the risk characterization for ground workers are the HQs. As summarized in Table 4-8, HQs range from 5.4 to 3,600 for workers, depending on the specific levels of exposure. As discussed in section 2, the HQ is simply the ratio of the estimated level of exposure to the RRV or some other index of acceptable exposure. This is a convenient benchmark in risk assessment because if the HQ is less than unity it would be generally accepted that there is no cause for concern. The limitation of the HQ, as illustrated in Table 4-8, is that exposure levels greater than the RRV or HQs greater than unity are not necessarily an indication that severe health effects are anticipated. This is the case for ground workers. Based on the study by Cook (1994), the health effects associated with the high HQs given in Table 4-8 can be classified as relatively mild and transient.

4.5.2.2. General Public and Aerial Spray Workers

As with the ground workers, the risk assessment for the general public is relatively direct. Epidemiology studies indicate that application rates as high as 20 BIU/acre have not been associated with adverse effects in humans. Consequently, this value has been adopted as the RRV. Unlike the risk characterization for ground workers, however, the risks associated with exceeding the RRV cannot be characterized directly. No epidemiology studies have been conducted at the maximum application rate of 40 BIU/acre. Thus, in Table 4-8, the HQ for this application rate is given as 2.

That an application rate of 40 BIU/acre would be associated with adverse effects in a human population does not seem likely. The differences between 20 BIU/acre and 40 BIU/acre are relatively small compared to the high variability in individual exposures, as illustrated in the monitoring data provided by the Oregon study, summarized in Table 4-6 and 4-7. For example, concentrations of B.t.k. at different road intersections after spraying varied from 0 to 4,200 cfu/m^3, with the lowest detectable level being 500 cfu/m^3 (Table 4-7). The difference between the lowest detected level and highest level is somewhat greater than a factor of 16. In addition, the exposure-severity relationships from the worker study suggest that levels of exposure much greater than the worker RRV are not associated with any clinically significant effects.

A separate risk characterization for aerial spray workers cannot be made because of the uncertainties associated with using cfu from the British Columbia study to estimate effects from the Oregon exposures, also expressed as cfu. As illustrated in Table 4-6, however, air crews are exposed to B.t.k. levels comparable to the levels of exposure for the general public.

4.5.2.3. Eye Irritation

Small amounts of commercial formulations of B.t.k. splashed into the eyes may cause eye irritation. The probabilities of this event occurring under various exposure scenarios (that is, number of hours worked) cannot be estimated from available data. Nonetheless, there have been four cases of eye irritation resulting from direct splashing of B.t. formulations in the eye. Thus, the probability of such an event seems sufficiently high to justify precautions when handling concentrated formulations in such a way that splashing into the eyes is a potential risk.

4.5.4. Cumulative Effects

The cumulative effects associated with the application of B.t.k. formulations must consider both the residual exposure to B.t.k. and formulation products after a single application as well as the effects of multiple applications in a single season and over several years. As

illustrated in the monitoring data from the Oregon study (Elliott and others 1986, 1988), levels of B.t.k. in air can be detected several days after spraying. Since the dose-response assessment is based on epidemiology studies, this type of cumulative effect is implicitly considered in the dose-response assessment. The effects of multiple exposures over several years cannot be assessed directly. As indicated by the British Columbia study (Noble and others 1992, Cook 1994), the anticipated effects are likely to be transient, in which case, cumulative effects from spray programs conducted over several years are not expected.

4.5.5. Connected Actions

Workers or members of the general public who are exposed to aerial or ground sprays of B.t.k. also will be exposed to the gypsy moth and may be exposed to other control agents. There are no data indicating that risks posed by these other agents will affect the response, if any, to B.t.k. formulations. Similarly, exposure to other chemicals in the environment may impact the sensitivity of individuals to B.t.k. or other agents. There are not, however, available data on which to base an assessment of the significance of such interactions.

4.5.6. Groups at Special Risk

B.t.k. formulations contain viable microorganisms; therefore, it may be reasonable to suggest that immunocompromised individuals may be at special risk. This was investigated and not reported in the British Columbia study (Nobel and others 1992). Animal studies using B.t.k. reported that immunocompromised mice cleared injected organisms in the same manner and without illness, compared with immunocompetent mice (Siegel and others 1987).

There is little information regarding groups with special sensitivities to B.t. formulations (for example, allergies or chemical sensitivities). In the British Columbia study on ground spray workers (Cook 1994), only a weakly positive relationship was noted in the incidence of irritant effects between ground workers with and without a history of asthma, seasonal allergies, or eczema.

Table 4-1. Commercial formulations of B.t.k. commonly used to control the gypsy moth

Formulation	Description
Abbott Laboratories	
DiPel 6AF/8AF	Water based suspensions; Density: 1.14 g/mL; Weight: 9.51 lbs/gallon; pH: 4.7; Contains surfactants; Sticker may be added after dilution; Droplet VMD between 50-150 μm; In deciduous forests, 96–128 oz/acre gives good control of the gypsy moth
DiPel 6AF	10,750 IU/mg or 48 BIU/gallon 21–107 oz/acre; 8–40 BIU/acre for the gypsy moth.
DiPel 8AF	14,500 IU/mg or 64 BIU/gallon 16–80 oz/acre; 8–40 BIU/acre for the gypsy moth.
DiPel 6L/8L	Emulsifiable oil-based suspensions; Disperse readily into water or oil-based carriers; Density: 0.94 g/mL; Weight: 7.84 lbs/gallon; Contains emulsifiers to ensure wettability; Stickers can be added to water prior to addition of Dipel; Droplet VMD between 50–150 μm; In coniferous forests, 12–30 BIU/acre will provide control of spruce budworm; in deciduous forests, 96–128 oz/acre gives good control of the gypsy moth
DiPel 6L	13,200 IU/mg or 48 BIU/gallon 2.6% ai, 97.4% inerts 21–107 oz/acre; 8–40 BIU/acre for the gypsy moth.
DiPel 8L	17,600 IU/mg or 64 BIU/gallon 16–80 oz/acre; 8–40 BIU/acre for the gypsy moth.

Table 4-1. Commercial formulations of B.t.k. commonly used to control the gypsy moth

Formulation	Description
Novo Nordisk	
Foray 48B	2.1% Btk, 97.9% inerts; 10,600 IU/mg 48 BIU/gallon 32–128 oz/acre recommended; 8–36 BIU/acre for gypsy moth
Foray 76B	3.3% active, 96.7% inert; 16,700 IU/mg; 76 BIU/gallon; 32–128 oz/acre; 8–40 BIU/acre for gypsy moth
Sandoz	
Thuricide 48LV	2.4% Btk, 97.6% inerts; 12,000 IU/mg; At least 18 million viable spores/mL; 12 BIU/quart; Adjuvants, spreaders, or stickers may be added but are not essential; 32–128 oz/acre recommended; Droplet sizes of 50–150 microns recommended; 22–106 oz/acre or 8–40 BIU/acre for gypsy moth
Thuricide 64LV	3.2% active, 96.8% inert; 16,000 IU/mg; At least 24 million viable spores/mL; 16.8 BIU/quart; Droplet sizes of 50–150 microns recommended; 16-80 oz/acre or 8-40 BIU/acre for gypsy moth;

Table 4-2. Toxicity of B.t.k. formulations to humans experimental animals

Chemical Formulation	Route of Exposure	Species/ Strain	No./Sex	Dose	Duration	Effects	Reference
Foray 76B	Inhalation	Rat/HSD	5/male 5/female	3.22 mg/L ($3.13x10^6$ CFU/L)	4 hours	Decreased activity, alopecia, piloerection, polyuria. Alopecia at necropsy was considered unusual and possibly related to exposure; no rats died during the study; during exposure period the rats were heavily coated with the thick test material.	Holbert 1991
Foray 48B		Rat/Sprague-Dawley	14/male 14/female	0.47 mg/L^{-1}	4 hours	Respiratory depression during exposure; wet and unkept appearance after exposure; gross pathology included mottled lungs (sometimes dark) in some rats; histopathology revealed alveolitis, interstitial pneumonitis, perivascular eosinophils and focal intra-alveolar hemorrhage. Only the rats' snouts were exposed to the test atmosphere; B.t.k. could be isolated from lung samples indicating that the formulation was respirable; B.t.k. was poorly eliminated from the lungs over a period of 28 days (no propagation occurred); the severity of the observed histopathology was predominantly minimal/mild, and the frequency and severity of the effects tended to decrease over time.	Oshodi and Macnaughtan 1990
Foray 48B		Rat/Sprague-Dawley	14/male 14/female	2.17 mg/L^{-1}	4 hours	Respiratory depression during exposure; wet and unkempt appearance after exposure; gross pathology included mottled lungs (sometimes dark) in a majority of rats; histopathology revealed alveolitis, interstitial pneumonitis, perivascular eosinophils and focal intra-alveolar hemorrhage; minimal bronchiolitis was observed in a few animals.	Oshodi and Macnaughtan 1990
Foray 48B		Rat/Sprague-Dawley	5/male 5/female	6.81 mg/L^{-1}	4 hours	Only the rats' snouts were exposed to the test atmosphere; there was no mortality; necropsy revealed no observable abnormalities; all values for lung:body weight ratio were within normal limits	McDonald and Scott 1991
Thuricide 32B		Rat/NS	NS	5.4 mg/L ($2.6x10^7$ spores/L)	NS	No mortality	U.S. EPA 1988b
B.t. (Berliner)	Oral	Human	5/male 5 female	1 g/day ($10x10^6$ viable spores/g)	3 days	No toxicity or infectivity; blood cultures negative; stool cultures positive after 3 days of exposure; GI tracts showed viable Bt in 5/10 individuals 30 days after exposure	U.S. EPA 1988b
Foray 48B		Rat/Sprague-Dawley	5/male 5/female	5000 mg/kg	single exposure	No mortality; no clinical signs; no abnormalities at necropsy	Cuthbert and Jackson 1991
Foray 76B		Rat/HSD	5/male 5/female	5050 mg/kg (4.49 mL/kg) [undiluted]	single exposure	No mortality; all rats appeared normal for the duration of the study; gross necropsy revealed no abnormalities in any of the rats	Kuhn 1991
Foray 48B		Rat/Wistar	14/male 14/female	1 mL	single exposure	No mortality; there was no treatment related pathology; after 4 days, B.t.k. was isolated from the lungs and spleen in one rat, which indicates a technical error at dosing; two other rats also showed the microorganism in the lungs after 15 and 22 days, respectively; the microbial count in feces decreased rapidly during the first 3 days after exposure.	Harde 1990
DiPel (NOS)		Rats/NS	NS	8400 mg/kg/day	13 weeks	None	Abbott Labs 1992
DiPel (NOS)		NS	NS	8400 mg/kg/day	2 years	None	Abbott Labs 1992

Table 4-2. Toxicity of B.t.k. formulations to humans experimental animals

Chemical Formulation	Route of Exposure	Species/ Strain	No./Sex	Dose	Duration	Effects	Reference
Thuricide 32B		Rat/NS	NS	$1.3x10^9$ spores/kg/day	13 weeks	No mortality or other signs of adverse effects.	U.S. EPA 1988b
Foray 48B	Intravenous	Rat/Wistar	5/male	1 mL ($3x10^9$ CFU/g) [vehicle=0.9% sterile NaCl]	single dose	Four of five rats died within 23 hours. Edema and hemorrhages were seen in the pyloric part of the stomach in all rats; two rats had enlarged spleens; the rat that was killed had a necrotic tail and extensive oedema and hemorrhages on the hindquarters stretching down on the hind legs.	Berg 1990
Foray 48B		Rat/Wistar	16/male 16/female	1 mL ($4x10^8$ CFU/rat) [vehicle=0.9% sterile NaCl]	single dose	No mortality; transient decreased motor activity and cyanotic appearance 30 minutes after exposure; enlarged spleen in 2 rats; treatment-related unspecific reactive hepatitis; A higher incidence of histopathological findings in the liver and the reticuloendothelial system was found in the treated group compared to the controls. These were attributed to a background infection with rat corona virus/sialodocryoadentitis virus and Bacillus piliformis, suggesting that the treatment with high levels of B.t.k. aggravated a preexisting disease. Over 167 days, a complete elimination of the test organism from all tissues except the spleen, which on average contained $3x10^2$ B.t.k./g at the end of the study	Berg 1990
Foray 76B	Dermal	Rabbit/New Zealand White	5/male 5/female	2.0 g ($1x10^{10}$ units/rabbit)	24 hours	No systemic effects; only mild skin reactions that cleared within 2 days after exposure. Behavior and appearance of all rabbits were normal throughout the study; agent was classified as "mild irritant"	Kiehr 1991
Foray 48B		Rabbit/Mol: Russian	6/female	0.5 mL	4 hours	Very slight erythema in one rabbit	Jacobsen 1993
DiPel 4L		Rabbit/NS	NS	1 mL/kg/day	21 days	Mild, transient irritation; no systemic toxicity	Abbott Labs 1992
DiPel 4L		Rabbit/NS	NS	7.2 g/kg	single application (NOS)	None	Abbott Labs 1992
Thuricide 32B		Rat/NS	NS	$3.4x10^{11}$ spores/kg	NS	No mortality; not toxic or infective effects; no effects on body weight or gross pathology. Study performed on intact and abraded skin.	U.S. EPA 1988b
Foray 48B (Batch BBN 6056)	Ocular	Rabbit/New Zealand White	6/male	0.1 mL	single application	Conjunctival reactions in the form of redness and discharge that cleared within 7 days after application	Berg 1991a
Foray 48B (Batch BBN 6057)		Rabbit/New Zealand White	6/male	0.1 mL	single application	Substantial conjunctival reactions; lesions were of temporary nature and cleared within 10 days after application	Berg and Kiehr 1991
Foray 48B (Batch BBN 6057)		Rabbit/New Zealand White	6/male	0.1 mL	single application	At day 7 mild redness was seen in 3/6 rabbits accompanied by small amounts of discharge in one of them; at day 8 mild redness was still seen in 1 rabbit and small of amounts of discharge were seen in another; lesions were temporary and cleared within 9 days after application.	Berg 1991b

NS = Not specified

Table 4-3. Exposure of ground spray workers to B.t.k.[a,b]

Position	Number of Samples	Range	Mean
Contractor A			
Sprayer	30	0.6–15.8	3.1
Hose	16	0.2–8.3	2.2
Auditor	30	0.4–9.6	2.0
Public relations	10	0.2–6.9	2.2
Contractor B			
Sprayer	8	0.9–10.5	5.9
Hose	6	0.6–4.0	1.7
Auditor	4	0.5–3.2	1.4
Public relations	2	0.6–0.7	0.7
Card handlers	3	0.2–0.6	0.3

[a]Source: Modified from Table 2 in Cook 1994

[b]Exposures expressed as millions of B.t.k. cfu per m^3 of sampled air.

Table 4-4. Symptom frequency in ground spray workers by B.t.k. exposure group[a]

Exposure Group[b]	Sex		Smoker		History[c]		Mask Used		
	Male	Female	Yes	No/ex-smoker	Positive	Negative	Regularly	Occasionally	Never
<1–100	1.4[d]	1.9	1.4	1.6	2.2	0.6	1.7	3.7	1.5
	0.7[e]	0.7	0.8	0.7	1.0	0.3	1.0	2.3	1.1
101–300	1.5	3.5	1.9	1.8	3.0	1.5	2.0	3.3	1.4
	1.0	2.3	1.3	1.2	2.4	1.0	1.7	3.3	0.4
>300	2.1	7.3	3.0	2.8	2.6	3.2	2.0	4.0	2.8
	1.9	5.8	2.3	2.6	2.4	2.5	2.0	4.0	2.3

[a]Source: Table 4 in Cook 1994

[b]Cumulative B.t.k. exposure in millions of cfu • hours

[c]Indicates preexisting medical condition

[d]Frequency of all symptoms reported by worker

[e]Frequency of symptoms attributed by the individual to Foray 48B B.t.k. exposure

Table 4-5. Reported symptoms of ground spray workers and controls exposed to B.t.k.[a,b]

Complaint (Site)	Controls (N=29)	Ground-Spray Workers (N=120)	
		Total	B.t.k. Attributed
Skin (dry, itchy)/ Chapped lips	10	34	25
Eyes (redness, itch, burning, puffiness)	13	20	19
Headache	10	7	3
Throat (dry, soreness)	7	29	22
Nose (runny)/Sinus (stuffiness)	13	27	17
Respiratory (cough, tightness)	3	20	12
Digestive (nausea, diarrhea)	10	7	4
Total	38	63	50

[a]Source: Table 3 in Cook 1994

[b]All values reported as percent of individuals with a positive response.

Table 4-6. Personal air samples for B.t. from June 1986, Lane County, Oregon monitoring study[a,b]

Job Title	cfu/Filter	Sample Volume (L)	cfu/m^3	Comments
Safety officer	53	14.6	3,600	Sample taken during office activities.
Helicopter pilot	6	4.5	1,300	Air vent on ship open.
Aerial observer	9	6.7	1,300	
Helicopter pilot	0	6.5	0	Air vent on ship closed.
Aerial observer	4	5.3	800	
Church custodian	0	8.7	0	During mowing of the church yard. Area had been sprayed 3 days prior.
Letter carrier	0	6.7	0	Route had been sprayed 3 days prior.
Card checker #3	0	14.7	0	Prior to placement of cards.
Card checker #1	5	11.7	400	During placement of cards.
Card checker #2	66	11.7	5,600	During placement of cards.
Card checker #1	12	21.1	600	During B.t. application. Card checker stayed out of spray.
Card checker #2	0	21.2	0	
Card checker #3	0	19.9	0	
Card checker #1	90	8.6	11,000	During card retrieval. Card checker was in brief direct contact with spray.
Card checker #2	6	8.4	700	During card retrieval. Card checker stayed out of spray.
Card checker #3	0	8.5	0	
Grocery store clerk	5	4.9	1,000	Facility within spray area. Monitored on same day as spraying. Individual not in direct contact with spray.
Service station attendant	7	4.3	1,600	
Security guard at gypsy moth project site	11	8.8	1,300	Individual not in direct contact with spray.

[a]Source: Modified from Table 5 in Elliott and others 1986

[b]All samples taken at a pump rate of 0.1 L/minute.

Table 4-7. General area air samples for B.t. from June, 1986 Lane County, Oregon, monitoring study[a]

Location	cfu/Filter	Sample Volume (L)[b]	cfu/m^3	Comments
Hotel room	0	5.5	0	Hotel room not in spray area on 6-2-86.
Mixing tank and pumping station project camp area	2	10.7	200	Mixing and pumping was not being conducted during sampling.
Batch truck at heliport loading area	0	6.1	0	
Restaurant parking area	2	4.0	500	Restaurant area had been sprayed 3 days prior.
Hotel room	0	15.5	0	Same location as on 6-2-86. This sample taken on 6-3-86.
Hotel parking lot	0	5.7	0	
School campus	0	8.5	0	School was within spray area.
Road intersections	57	13.5	4,200	Sample collected after spraying was concluded.
	0	8.9	0	Sample collected during spraying.
	0	13.2	0	Sample collected after spraying.
	3	6.2	500	Sample collected after spraying.
Hotel room	7	3.7	1,900	Same location as on 6-2-86. This sample taken on 6-4-86. Probably due to contamination, as discussed by Elliott and others 1988.

[a]Source: Modified from Table 6 in Elliott and others 1988

[b]Pumping rates not specified.

Table 4-8. Risk characterization of respiratory, dermal, and eye irritation associated with exposures to commercial formulations of B.t. suspended in the air.

Type of Estimate	Exposure[a]	Hazard Quotient[b]
Ground Workers/Sprayers - Low Exposure Group		
Low estimate	5.4	30
Central value	20	100
High estimate	100	500
Ground Workers/Except Sprayers - Medium Exposure Group		
Low estimate	101	500
Central value	175	900
High estimate	300	1500
Ground Workers/Except Sprayers - High Exposure Group		
Low estimate	301	1500
Central value	465	2400
High estimate	720	3600
General Public		
Low estimate	20 BIU/acre	1
High estimate	40 BIU/acre	2

[a] For workers = cfu cumulative exposure
For general public = application rates in BIU/acre

[b]RRV for workers = 0.2 cfu cumulative exposure
RRV for public = 20 BIU/acre

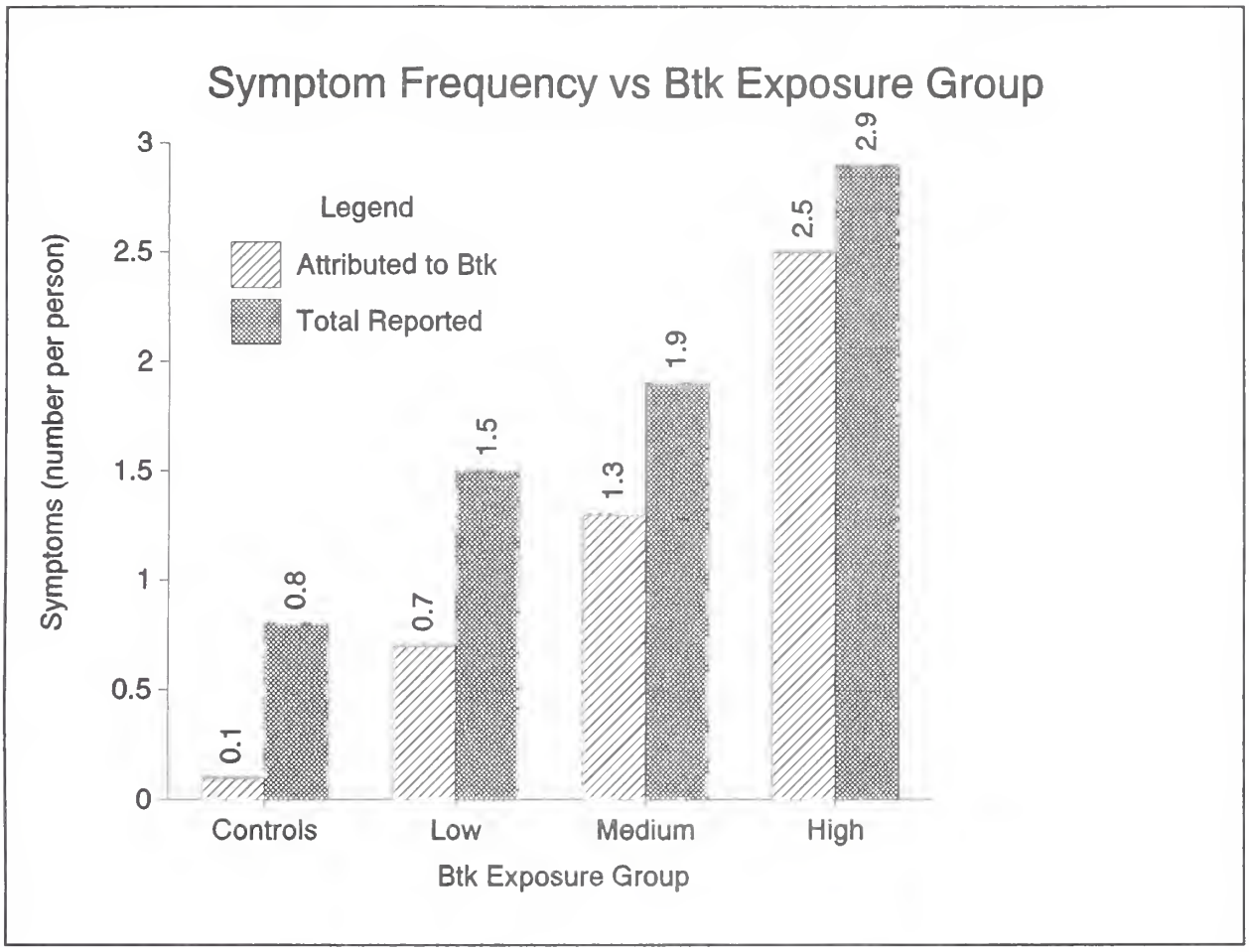


Figure 4-1: Average Number of Symptoms Reported by Workers Exposed to Foray 48B and a Control Group not Exposed to Foray 48B (modified from Cook, 1994). For ground workers involved in the application of B.t.k., there is a positive association between exposure and the number of symptoms/person. The responses are irritation to the skin, eyes, and respiratory tract. There was no increase in the number of workdays lost for ground workers, compared to individuals in the control group.

5. Nucleopolyhedrosis Virus

5.1. Program Description

Gypsy moth nucleopolyhedrosis virus (NPV) is a naturally occurring baculovirus that is usually important in bringing about the collapse of gypsy moth populations (Podgwaite 1979). Gypchek is a powdered formulation of NPV developed and registered by USDA for control of the gypsy moth. The powder is produced by culturing and processing gypsy moth larvae infected with NPV. The active ingredient in Gypchek is 20% (by weight) occlusion bodies (OB) of NPV. The OB are occluded virus particles containing variable numbers of nucleocapsids (genetic material) within one protein envelope. The remaining 80% of the Gypchek formulation consists of gypsy moth parts. A similar product, Disparvirus, was developed in Canada (Nealis and Erb 1993). Gypchek causes polyhedrosis, a viral disease of insect larva, which is characterized by dissolution of tissues and the accumulation of polyhedral granules in the resultant fluid.

Gypchek is usually applied against first or second instars of the gypsy moth. The recommended standard application parameters are 1 gallon/acre per application, two applications 3–5 days apart at $2 \cdot 10^{11}$ OB/acre per application. For eradication efforts, the maximum application is $1 \cdot 10^{12}$ OB/acre per application. In all applications, the Gypchek formulation is applied at particles sizes of 100–150 μ (Podgwaite 1994).

Gypchek is not used as much as other gypsy moth control agents such as B.t.k. and diflubenzuron. From 1980 to 1993, Gypchek was applied to less than 24,000 acres; B.t.k. was applied to approximately 5.3 million acres; diflubenzuron was applied to approximately 3.7 million acres to suppress gypsy moth infestations (U.S. Department of Agriculture, Forest Service 1994a).

Three applications of Gypchek, all aerial, are recorded in the APHIS database on gypsy moth eradication projects: 425 acres in Waukesha County, Wisconsin in 1979; 50 acres in Warren County, North Carolina in 1990; and 91 acres in Hamilton and Warren Counties in 1991. The Forest Service uses Gypchek in suppression programs. This use increased from less than 50 acres in 1988 to more than 12,000 acres in 1992. Only about 6,000 acres were treated with Gypchek in these programs in 1993 (Reardon and others 1993).

Ground applications of Gypchek were part of the Maryland Integrated Pest Management Gypsy Moth Project, 1983-1987. Field studies in which Gypchek was applied to egg masses using mist blowers and hydraulic equipment indicated that these applications are ineffective partly because of the low level of persistence of NPV (Reardon and others 1993). Ground applications against first and second instars were effective in decreasing moderate to dense populations (Podgwaite and others 1991, Reardon and others 1993).

Recently, the Forest Service tested a genetically engineered gypsy moth virus (McManus 1993). This virus strain is not proposed for general application; consequently, it is not considered in this risk assessment.

5.2. Hazard Identification

Data regarding health effects in humans after exposure to NPV were not located in the available literature. Most of the mammalian toxicity data on Gypchek are unpublished, but were submitted to the U.S. EPA by USDA as part of the registration package. The complete registration package and all of the available published studies were reviewed during the preparation of this risk assessment. Unlike the toxicity data on the other agents covered in this risk assessment, the toxicity data on Gypchek have not been reviewed in detail in the published literature. Consequently, the discussion of the potential toxic effects of Gypchek is followed by a relatively detailed description of the available data. These data indicate that Gypchek may be an eye irritant and, possibly, a dermal irritant. No other effects (that is, systemic toxicity or infectivity) seem plausible.

5.2.1. Overview

Dose units for Gypchek may be expressed as weight of virus or OB per unit of surface, weight, or volume. The average mass weight of a polyhedra is $3.66 \cdot 10^{-12}$ g or $3.66 \cdot 10^{-9}$ mg, based on 250 individual measurements (Mazzone n.d.). The dose of gypsy moth parts in units of weight is 4 times the dose of NPV expressed in a unit of weight (80% ÷ 20% = 4). The corresponding dose of Gypchek powder in units of weight is 5 times the dose of NPV expressed in a unit of weight

$$100\% \div 20\% = 5.$$

In this risk assessment, toxicity data are converted to units of mg Gypchek powder, using the relationships discussed above.

A series of experiments in which immunosuppressed mice and guinea pigs were exposed to Gypchek indicate that the insecticide is not likely to be infectious or cause extraordinary effects in individuals with compromised immune functions. By analogy to the human health effects of the gypsy moth, individuals who have preexisting allergies may be at greater risk than others to any effects of Gypchek associated with the gypsy moth parts. Incidental contamination of Gypchek may be of potential concern; however, each batch is tested for contamination before use.

Acute, subchronic, and chronic oral toxicity tests in experimental mammals have not identified toxic levels of Gypchek at doses up to 3,200 mg Gypchek/kg body weight. A NOEL of 45 mg Gypchek/kg body weight in rats was determined in a 2-year feeding study.

The lack of oral toxicity in experimental mammals is supported by feeding and field studies in wildlife.

Given that Gypchek contains 80% (w/w) gypsy moth parts and that exposure to the gypsy moth has been associated with respiratory effects in humans (see section 3 on the gypsy moth), respiratory irritation at some level of exposure seems plausible. The plausibility of Gypchek causing such an effect is supported by animal data. Rats exposed to 6.12 mg/L (6,120 mg/m^3) were inactive and had labored respiration. In addition, eye irritation might be inferred because the animals kept their eyes shut. There was no indication, however, of any systemic or respiratory pathology. No adverse effects have been observed in animals exposed to Gypchek doses ranging from 0.028 to 0.81 mg/L.

Dermal exposure to the gypsy moth has been associated with skin irritation in humans; however, this effect was not observed in rabbits in two skin irritation studies. Because the human responses to dermal exposure to the gypsy moth may be an allergic reaction, the relevance of the negative findings in experimental mammals may be limited.

Gypchek has been shown to cause eye irritation in experimental mammals (section 5.2.6). This is consistent with the human health effects of exposure to gypsy moth parts (see section 3). A 3 mg concentration of Gypchek powder applied to one eye of rabbits caused mild conjunctival irritation, preventable by washing (Cannon Laboratories, Inc. 1976a). Exposure concentrations of 50 mg caused effects on the cornea and iris, which, under the conditions of the experiment, were not eliminated by washing the eye shortly after exposure (Litton Bionetics, Inc. 1977).

5.2.2. Treatment Formulations

5.2.2.1. Contaminants and Pathogenicity

In response to the potential for Gypchek to become contaminated with bacteria, a quality control program has been developed to ensure that batch preparations of NPV do not contain harmful bacteria (Podgwaite and Bruen 1978). The program consists of tests to determine bacterial counts of total aerobes, anaerobes, and bacterial spores; an enumeration of total and fecal coliform bacteria, assays for primary pathogens (that is, Salmonella, Shigella, Vibrio, Streptococcus, Staphylococcus, and Clostridium) and an in vivo pathogenicity test in mice. These tests are performed on each batch of Gypchek before it is used.

A series of experiments was conducted to determine if NPV could infect or otherwise affect mice immunosuppressed with cyclophosphamide, thymectomy, or anti-lymphocyte serum and guinea pigs immunosuppressed with cortisone or cobra venom factor. No lesions, histopathological changes, or signs of infection associated with treatment were noted (Shope and others 1977). Consistent with the results of experimental studies on Heliothis NPV

(Ignoffo and others 1977), the pathogenicity of gypsy moth NPV to gypsy moth larva is destroyed or eliminated within 72 hours after oral administration of a large dose to rats. Some viable NPV remained in the liver on days 0, 1, and 14 (Litton Bionetics, Inc. 1977).

USDA funded a study entitled, Gypsy Moth Virus: Enzyme and Specificity Studies, at the Waksman Institute of Microbiology of Rutgers University. The final progress report of this study indicates that inoculation of the virus into vertebrate cell lines sometimes decreased the rate of cell growth. The decreased growth rate persisted after several subcultures without further virus inoculations (Padhi 1978), which suggests that the virus may cause permanent changes in the cells. This study has not been published, and other studies of this nature were not located in the available literature.

Circulating antibodies to the insect viral subfractions have not been observed in laboratory workers (Mazzone and others 1976, Tignor and others 1976).

5.2.2.2. Inerts

Gypchek is applied in a commercially developed carrier. Each application consists of 5% of a Gypchek slurry and 95% carrier. The carrier used in the 1994 application is being modified as this risk assessment is under preparation (Podgwaite 1994). Various modifications are being tested by Entotech, Inc. and a carrier for the 1995 program will not be selected until October 1994. Although the specific components in the carrier are proprietary and a final selection of the components has not been made, all of the components are on EPA List 4 (see section 2) and all are exempt from residue tolerances under Chapter 40 of the Code of Federal Regulations, Section 180.1001 (Hobbs 1994). As with the inerts in B.t.k. formulations, most of the components are natural products, many of which are complex and not chemically defined. The exact composition will vary over time as different sources of the material are used.

5.2.3. Oral Toxicity

No adverse effects in animals have been observed after acute, subchronic, or chronic exposure to Gypchek. In a single dose study with a 30-day observation period, each rat was exposed to an oral dose of 400 mg Gypchek (Cannon Laboratories, Inc. 1976b). The body weights of the rats ranged from 100 to 150 g, which means that the dose corresponding to the average body weight (125 g) was 3,200 mg Gypchek/kg body weight. An equal number of control rats was used. All animals survived, and there were no remarkable differences in pathology between the exposed and control groups. According to the study, "The animals exposed to 'Gypsy Moth NPV' received the test material equivalent to their body weight at the same dose level that a 70 kg man would receive at 100 times the field dose per acre." The study does not explain how the authors arrived at this estimate.

In a similar study, rats were exposed to oral doses of $40 \cdot 10^9$ polyhedra/rat (Litton Bionetics, Inc. 1975), which corresponds to a dose of approximately 750 mg Gypchek/rat. The initial body weight of the rats was approximately 200 g; thus, this dose corresponds to 3,750 mg Gypchek/kg body weight. The rats were observed daily for appearance and mortality. Body weights and food consumption were recorded weekly. Blood glucose and SGPT were measured on days 0 and 21. On days 0, 14, and 21, blood samples were assayed. Partial sacrifices were made on days 0, 1, 7, 14, 21, and 35. Standard pathology examinations were conducted, and no significant or otherwise remarkable differences were noted between control and treated animals.

Purebred beagles were given daily doses of 0, 10^7, 10^8, and 10^9 OB of NPV/dog in a 90 day feeding study. These doses correspond to Gypchek doses of 0, 1.8, 18, and 180 mg/dog. The terminal body weights reported in the study were 9.5 kg for low dose group, 11.1 kg for the middle dose group, and 10.3 for the high dose group. These doses expressed in mg Gypchek/kg body weight equal 0.2 for the low dose group, 1.6 for the middle dose group, and 17 for the high dose group. Each dog was observed at least once daily for gross effects. Standard hematology, clinical biochemistry, and urinalysis were conducted on each animal at or before the start of exposure and at 2, 4, and 6 months after the start of exposure. After sacrifice, standard examinations were conducted for signs of gross pathology or histopathology. No treatment related effects were observed (Litton Bionetics, Inc. 1975)

In a 2-year feeding study, Dublin (that is, Sprague-Dawley derived) rats were given NPV in chow at levels that resulted in daily doses of 10^7 or 10^8 OB/rat. This corresponds to Gypchek daily doses of 1.8 or 18 mg/rat. The average terminal body weights (both sexes combined) was approximately 400 g. Thus, the dose rate was 4.5 or 45 mg Gypchek/kg body weight. Each of the treated and control groups consisted of 50 males and 50 females. Observations included body weight, food consumption, gross signs of toxicity, and pathology. No increased mortality was observed. No pathological changes were attributed to treatment (Litton Bionetics, Inc. 1975).

Oral toxicity studies in wildlife support the data on experimental mammals, indicating that Gypchek has a very low oral toxicity. White footed mice, shrew, and opossum were fed NPV intermittently over an 18-day period (Lautenschlager and others 1977). No adverse effects on general health, reproductive efficiency, gross pathology, or histopathology were noted. The investigators report that the exposure rates were equivalent to a greater than 40-hectare exposure for a 70 kg person, assuming the NPV was applied at the rate of $5.0 \cdot 10^{11}$ OB/hectare. No further details regarding these estimates are provided.

5.2.4. Inhalation Toxicity

Two acute inhalation studies have been conducted on Gypchek, and neither of them gives a direct indication of toxic effects. In one study, no overt signs of toxicity were observed in a group of 10 male rats exposed to 6.12 mg/L Gypchek for 1 hour. During exposure, the rats

were inactive and had closed eyes and labored respiration. Examinations for lung and trachea pathology 1, 7, and 14 days after recovery revealed no effects attributable to exposure (Cannon Laboratories, Inc. 1976c). In the other inhalation study, rats were subjected to heads only exposure to avoid ingestion during grooming (Litton Bionetics, Inc. 1975). The test material was a white dust with $1.76 \cdot 10^{11}$ OB/g. The exposure concentrations ranged from 0.028 to 0.81 mg/L. No signs of toxicity were observed in any of the rats during exposure or upon necropsy.

5.2.5. Dermal Toxicity and Irritation

Gypchek was applied to the intact and abraded skin of rabbits at a dose of 1 g test material/application over approximately 10.7% of the animals' body surface. Observations were made daily for 21 days. Gross pathology of the skin and other organs was conducted at the end of the study. No mortality, abnormal behavior, or pathology were observed (Cannon Laboratories, Inc. 1976d). Skin irritation was assayed in six New Zealand white rabbits (Litton Bionetics, Inc. 1975). Gypchek was suspended in 0.8% saline at the rate of $40 \cdot 10^9$ polyhedra/rabbit, which corresponds to a dose of approximately 260 mg/rabbit. The material was applied to the skin and covered with a 1" square gauze patch. The patch was protected by a nonabsorbent binder. No irritation was observed in intact or abraded skin, and there was no evidence of systemic toxicity.

5.2.6. Eye Irritation

Gypchek caused eye irritation in six New Zealand albino rabbits exposed to 20 mg of NPV in the left eye, with the untreated right eye serving as a control. Observations were made after 1, 2, 3, 4, and 7 days. All six rabbits exhibited a positive reaction at all observation periods; moreover, four of the rabbits had corneal involvement at all observation periods (Cannon Laboratories, Inc. 1976e).

In a similar study, six New Zealand albino rabbits were exposed to 3 mg of NPV in the left eye, with the untreated right eye serving as a control. For two of the rabbits, the eyes were washed after 1 minute. For two other rabbits, the eyes were washed after 5 minutes. The eyes of the remaining rabbits were not washed. Observations were made after 1, 2, 3, 4, and 7 days. Rabbits whose eyes were washed exhibited no irritation; slight conjunctival irritation was observed in the rabbits whose eyes were not washed (Cannon Laboratories, Inc. 1976a).

In another ocular toxicity test using New Zealand white rabbits, a fluorescein test was performed to detect preexisting corneal damage. Irritation in a 10-second wash group (that is, a group in which the eyes were washed 10 seconds after exposure) was limited to conjunctival redness lasting through day 4. One rabbit in this group had a Staph infection in the test eye at the 4-day microbiological evaluation. All rabbits in the 1-minute wash group

had signs of conjunctival redness of grade 2 at the 24-hour grading. At 48 hours, all rabbits showed a grade 1. All irritation cleared after 4 days. Corneal opacity and irritation of the iris (iritis) was observed in the 5-minute and no wash groups. Corneal opacity was still observed at 14 days in all but one rabbit in the no wash group (Cannon Laboratories, Inc. 1978).

Ocular toxicity tests in New Zealand white rabbits were also conducted on a batch of Gypchek specified as: "Lot 35, a light gray powder labelled 6.48×10^{10}/gram". One eye of each rabbit was treated with 50 mg of the compound. Washes (20 mL deionized water) were conducted at 1 and 5 minutes after installation in three of the nine rabbits. Examinations were conducted at 1, 2, 3, 4, 7 and 14 days. On days 7 and 14, treated eyes were examined again with fluorescein dye to confirm the absence of corneal damage. Scattered or diffuse areas of corneal opacity were observed in one or more rabbits from each of the three groups. By day 14, three rabbits still showed signs of corneal opacity, two from the 5-minute wash group and one from the no wash group. The iris in one rabbit from the no wash group was affected (Litton Bionetics, Inc. 1977).

5.3. Exposure Assessment

As indicated by the hazard identification (see section 5.2), dermal and inhalation exposures are of potential concern to workers and the general public. During aerial and ground applications both workers and the general public are subject to a combination of dermal and inhalation exposure to Gypchek, with the possibility of incidental oral exposure.

Neither personal nor general air monitoring data for workers or the general public are available. There are methods for estimating worker exposure to chemicals based on the amount of material handled and the worker's job category (see section 2.2); however, these methods are not applicable to biological agents.

As an approximation, the nominal application rate will be used to estimate potential air exposures. The maximum application rate of $1 \cdot 10^{12}$ OB/acre is equal to $2.48 \cdot 10^{8}$ OB/m^2

$$1 \cdot 10^{12} \text{ OB/acre} \div 4{,}047 \text{ m}^2\text{/acre} = 2.48 \cdot 10^{8} \text{ OB/m}^2.$$

Assuming that the application is made at a height 50 feet or 15.2 meters and that complete and instantaneous mixing takes place, the concentration in air would be $1.6 \cdot 10^{7}$ OB/m^3

$$2.48 \cdot 10^{8} \text{ OB/m}^2 \div 15.2 \text{ m} = 1.6 \cdot 10^{7} \text{ OB/m}^3.$$

This would amount to 0.06 mg NPV/m^3

$$1.6 \cdot 10^{7} \text{ OB/m}^3 \cdot 3.66 \cdot 10^{-9} \text{ mg/OB} = 0.06 \text{ mg NPV/m}^3$$

or 0.3 mg/m^3 Gypchek. This is not to suggest that complete and instantaneous mixing will occur. Rather, this calculation may be regarded as a time-weighted average concentration in a column of air during deposition of Gypchek, ignoring dispersion.

The duration of exposure can be approximated using the FSCBG model. Model parameters for this estimate include an aircraft height of 78 feet, a speed of 110 miles/hour, the use of Micronair Au 5000 nozzles at 2,700 rpm, a temperature of 70°F, a relative humidity of 85%, and a wind speed of 3 miles/hour. Under these conditions, times to particle impact range from approximately 1 to 2 minutes.

Dermal exposure to Gypchek can be estimated only from deposition rates. Given the nominal application rates of $2.48 \cdot 10^8$ OB/m^2 and assuming $3.66 \cdot 10^{-9}$ mg/OB, this corresponds to 0.9 mg NPV/m^2

$$2.48 \cdot 10^8 \text{ OB/m}^2 \cdot 3.66 \cdot 10^{-9} \text{ mg/OB} = 0.9 \text{ mg NPV/m}^2$$

or 4.6 mg Gypchek/m^2.

An oral exposure assessment does not seem warranted. Oral exposure is likely to be incidental to dermal and inhalation exposure.

5.4. Dose-Response Assessment

Decreased activity and labored respiration have been observed in experimental mammals during 1 hour of inhalation exposure to 6,120 mg Gypchek/m^3 (Cannon Laboratories, Inc. 1976c). Although no effects were observed after exposure, this concentration may be regarded as an AEL. NOELs for these effects range from 0.028 mg Gypchek/L to 0.81 mg/L. The geometric mean of these values, which can be used as a measure of central tendency, is 0.15 mg Gypchek/L (150 mg Gypchek/m^3). This NOEL may be divided by an uncertainty factor of 100 (10 for species extrapolation and 10 for sensitive individuals) to yield a short-term respiratory RRV of 1.5 mg Gypchek/m^3.

The available data on dermal irritation are not adequate for a dose-response assessment. Eye irritation has been observed after direct application of Gypchek concentrations as low as 3 mg/eye. Although positive dose-severity effects have been demonstrated, a NOEL for eye irritation has not been demonstrated.

Oral toxicity, which is not a primary concern in this risk assessment, has been well characterized in experimental mammals. Toxic oral doses of Gypchek have not been identified. NOELs for short-term exposure to as much as 3,200 mg Gypchek/kg body weight have been reported, and the highest NOEL for chronic oral exposure is 45 mg Gypchek/kg body weight, from a rat feeding study. Using standard methods (see section 2.5), a chronic oral RRV for Gypchek can be derived by dividing the chronic NOEL of 45

mg Gypchek/kg body weight/day by an uncertainty factor of 100 (10 for species extrapolation and 10 for sensitive subgroups). Thus, the oral RRV is 0.45 mg/kg body weight/day. The use of this RRV for applications of Gypchek would be highly conservative because it represents a daily dose that is not expected to cause adverse effects over a lifetime exposure. An acute RRV of 32 mg/kg/day can be derived based on the acute NOEL of 3,200 mg Gypchek/kg body weight, using the uncertainty factor of 100.

5.5. Risk Characterization

Gypchek, like commercial formulations of B.t.k., may be applied by aerial spray over relatively large areas; therefore, exposure may affect both workers and the general public. As with commercial formulations of B.t.k., the active ingredient in Gypchek is a biological agent. Unlike commercial formulations of B.t.k., Gypchek has not been used extensively, so human experience with this agent is limited. There are no epidemiology, clinical, or anecdotal data regarding the human health effects of Gypchek exposure. Furthermore, monitoring studies have not been conducted on Gypchek levels in air after aerial application, and there are no data regarding worker exposure to the agent.

Based on recommended application rates, conservative exposure assumptions and available animal toxicity data, risks to both workers and the general public seem minimal. Eye irritation may be an effect of concern for workers if the material is splashed directly into the eyes. Whether or not this is an effect of concern for the general public is far less certain.

5.5.1. Uncertainties.

The major uncertainties in this risk assessment are associated with the lack of human toxicity and exposure data. Because Gypchek contains approximately 80% gypsy moth parts, it seems reasonable to expect that the clear and well documented toxic effects associated with human exposure to gypsy moth larvae might be observed after human exposure to Gypchek.

This is not to say that Gypchek applications will significantly increase the levels of gypsy moth parts in the environment. The average yield from the laboratory strain used to produce Gypchek is $1.5 \cdot 10^9$ OB (Podgwaite 1994). Thus, the maximum recommended application rate of $1 \cdot 10^{12}$ OB/acre corresponds to approximately 667 larvae equivalents:

$$1 \cdot 10^{12} \text{ OB/acre} \div 1.5 \cdot 10^9 \text{ OB/larva} = 667 \text{ larvae.}$$

During gypsy moth outbreaks, 10,000–100,000 larvae/acre usually survive to late instars (instars 4-6). In general, at least 50% of these (5,000–50,000) succumb to NPV. Thus, the maximum application rate corresponds to only 1.3%–13% of the OB deposited in a site during a natural gypsy moth outbreak. Moreover, it is not clear that Gypchek contains a significant quantity of the gypsy moth material that elicits toxic effects in humans. The

available data on human exposure to the gypsy moth indicate that the early instars are most often associated with adverse effects in humans (see section 3.2). Gypchek is produced primarily from later stage and much larger larvae. Although these larvae may have toxic or allergenic activity (see section 3.2), it is not clear whether the toxic or allergenic agents persist, and, if they do, at what levels they are present in Gypchek. This uncertainty can be resolved by a simple clinical study using a standard patch test to determine if Gypchek is allergenic to individuals with a known sensitivity to the gypsy moth or if Gypchek causes dermal effects in individuals who are or are not sensitive to gypsy moth exposure.

The other major uncertainty concerns the exposure assessment. As noted with commercial formulations of B.t.k., airborne exposures can be prolonged, with significant amounts of B.t.k. found in air several days after exposure (see section 4.3). The same phenomenon may or may not occur after Gypchek applications. This uncertainty can best be resolved by one or more monitoring studies, which, if designed to provide individual air monitoring of workers, might be directly useful for the worker exposure assessment.

Other endpoints of special concern for all agents covered in this risk assessment include teratogenicity, carcinogenicity, and effects on reproductive capacity. Based on the chronic oral feeding study, there is no evidence for carcinogenicity. Because this is based on only a single study in a single species, the database would be classified as "Inadequate" according to the U.S. EPA (1987a) or International Agency for Research on Cancer (IARC) schemes. Wildlife studies suggest that teratogenic or reproductive effects are unlikely.

5.5.2. Workers and the General Public

For the general public, low risks are associated with inhalation, dermal, or oral exposure to Gypchek at application rates as high as the maximum proposed rate of $1 \cdot 10^{12}$ OB/acre.

As discussed in the exposure assessment (see section 5.3), air concentrations as high as 0.3 mg Gypchek/m^3 are plausible at an application rate of $1 \cdot 10^{12}$ OB/acre, assuming instantaneous mixing in a 50-foot column of air. The duration of exposure is estimated at 1–2 minutes. The acute inhalation RRV for Gypchek, based on a 1-hour exposure period, is 1.5 mg/m^3. The endpoints covered by this RRV include respiratory irritation, eye irritation, and general toxic effects. For many compounds, risks related to inhalation exposure are assumed to be a simple product of concentration and duration. This is referred to as Haber's law. Under this assumption and using a 2-minute duration of exposure, the HQ is 0.006

$$(0.3 \text{ mg/m}^3 \cdot 2 \text{ minutes}) \div (1.5 \text{ mg/m}^3 \cdot 1 \text{ hour} \cdot 60 \text{ minutes/hour}).$$

Concern could be expressed that Haber's law is not applicable in this case because the effects of concern involve irritation; in which case, concentration may be the most important factor. In view of this argument, the mixing depth of the plume would have to be approximately 2.5 feet to achieve a concentration of 1.5 mg/m^3. The short-term inhalation AEL is about 6,120

mg/m^3. Dividing this value by an uncertainty factor of 100 to obtain a level of concern yields about 60 mg/m^3. To achieve this concentration would require a mixing depth for the plume of only 3 inches, which is clearly implausible. Consequently, whether or not Haber's law is assumed, it is unlikely that aerial sprays of Gypchek at application rates as high as $1 \cdot 10^{12}$ OB/acre will be associated with respiratory tract or eye irritation. Using Haber's law, an application rate of $1.7 \cdot 10^{14}$ would be required to reach an HQ of unity ($1 \cdot 10^{12}$ OB/acre $\div$ 0.006). Even at this application rate, the endpoints involved in the risk assessment would be transient irritation with no signs of systemic toxicity.

The potential for dermal effects is somewhat problematic. Dermal irritation has not been observed in rabbits exposed to concentrations as high as 1 g of test material applied to approximately 10.7% of the body surface or at $4 \cdot 10^{10}$ polyhedra/animal for intact or abraded skin. This seems greater than any plausible dermal exposure for the general public. At an application rate of $1 \cdot 10^{12}$ OB/acre, the NOEL of $4 \cdot 10^{10}$ polyhedra/animal represents about 5% of the total dose/acre. Effect levels for skin irritation have not been identified. Nonetheless, exposure to the gypsy moth has been associated with dermal effects in humans. Because Gypchek contains a substantial amount of gypsy moth parts, dermal effects might be anticipated. The lack of dermal effects in laboratory animals may indicate that the species tested are insensitive. This uncertainty in the risk assessment cannot be quantified without additional experimental data, and no quantitative characterization of risk is possible.

Although oral exposure is not of primary concern to this risk assessment and a quantitative exposure assessment has not been made, the presumption that this route is inconsequential can be assessed. The maximum application rate of $1 \cdot 10^{12}$ OB/acre corresponds to approximately 18,300 mg/acre Gypchek

$$1 \cdot 10^{12} \text{ OB/acre} \cdot 3.66 \cdot 10^{-9} \text{ mg/OB} \cdot 5 = 18{,}300 \text{ mg/acre.}$$

Using the acute oral RRV of 32 mg/kg and assuming an adult male body weight of 70 kg, an RRV equivalent is applied to each 0.122 acres

$$70 \text{ kg} \cdot 32 \text{ mg Gypchek/kg} \div 18{,}300 \text{ mg Gypchek/acre} = 0.122 \text{ acres}$$

or approximately 500 m^2

$$0.122 \text{ acres} \cdot 4{,}047 \text{ m}^2\text{/acre} = 495 \text{ m}^2.$$

Thus, at this RRV, an adult would have to consume all of the Gypchek applied to 500 m^2 in order to reach the acute RRV. For a 10 kg child, an RRV equivalent is applied to each 73 m^2. Even if these levels were consumed, which seems highly implausible, there is no evidence that exposure would approach a toxic threshold.

There are no data from which to assess exposure or potential risks to workers. This is a limitation of the risk assessment. By analogy to commercial formulations of B.t.k. and other pesticides, workers, especially those involved in ground applications, are more likely than the general public to be exposed to high levels of Gypchek. The effects of concern would be similar to those for commercial formulations of B.t.k., including eye, skin, and respiratory tract irritation. No assessment, however, can be made regarding the likelihood of any of these effects being observed.

5.5.3. Cumulative Effects

Given the low level of apparent risk associated with a single application of Gypchek at the maximum application rate, there is no reason to anticipate that repeated exposures, either during a spray season or over multiple spray seasons, will result in any appreciable increase in risk. This assessment, however, must be tempered by the uncertainties associated with a lack of any toxicological data on humans. Because Gypchek contains gypsy moth parts and because there is a suggestion that some individuals may have allergic reactions to the gypsy moth (section 3.2.1), allergic reactions to Gypchek are plausible but speculative.

5.5.4. Connected Actions

It is not possible to assess the consequences of connected actions involving the various program activities or other common activities, given the available data. Nonetheless, because Gypchek contains gypsy moth parts and may cause irritant effects similar to those caused by the gypsy moth, exposure to both gypsy moth larvae and Gypchek might be additive. This assessment, however, is based on speculation.

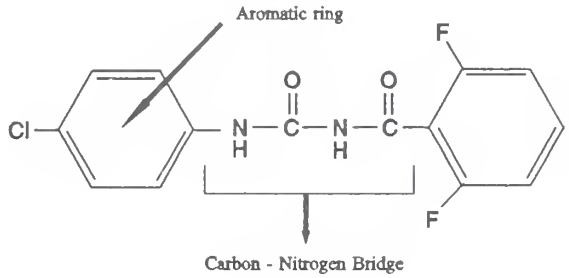
5.5.5. Groups at Special Risk

As discussed in the hazard identification (see section 5.2), the available data do not suggest that immunocompromised animals are at increased risk. By analogy to the human health effects of the gypsy moth (see section 3.2), individuals with preexisting allergies may be at greater risk than others to the human health effects of Gypchek associated with gypsy moth parts.

6. Diflubenzuron

6.1. Program Description

Diflubenzuron (DFB) [1-(4-chlorophenyl) 3-(2,6-difluorobenzoyl)urea] is an insecticide that inhibits chitin deposition. Chitin is a polymer (repeating series of connected chemical subunits) of a glucose-based molecule and comprises a substantial proportion of the exoskeleton (outer-shell) of insects. Consequently, the inhibition of chitin synthesis disrupts the growth and development of insects (Post and others 1974). The molecular structure of DFB is:



DFB is registered by Duphar B.V. and distributed by Uniroyal Chemical Corporation under the trade name of Dimilin in two formulations, 25W and 4L. Uniroyal Chemical Company has announced that it is eliminating Dimilin 25W from forestry uses, beginning in 1994 (Uniroyal 1994). As noted in this announcement, existing inventories of Dimilin 25W labelled for forestry use still may be applied. Dimilin has been used also to control various lepidoptera in cotton, soybeans, forests, apples, pears, stone fruit, and other horticultural crops. In addition, Dimilin is effective against mosquitoes, midges, various weevils and flies, and leafminers (Nigg and others 1986).

For Dimilin 25W and Dimilin 4L, the recommended application rates for the control of the gypsy moth range from 7 to 28 g ai/acre. In any year as many as three applications may be made, but the total annual application cannot exceed 28 g ai/acre. In general, USDA anticipates using two applications of 14 g ai/acre for each application. In this risk assessment, all exposures are based on a single application at the maximum allowable rate of 28 g ai/acre. As detailed in the section on cumulative effects (section 6.5.5), this approach encompasses the risks associated with multiple applications at lower rates.

Whereas some applications may be made in relatively remote areas involving limited exposure to the general public, aerial and ground applications may be made in residential areas. Consequently, risks for both workers and the general public must be assessed.

6.2. Hazard Identification

6.2.1. Overview

The oral toxicity of DFB has been characterized relatively well. Most of the studies were conducted during the 1970s and in the early 1980s, coinciding with the commercial development and early use of Dimilin. The dermal toxicity of Dimilin is not well characterized. Standard acute dermal studies indicate that DFB is poorly absorbed, and, therefore, is not likely to cause gross toxic effects by this route of exposure. Since the vapor pressure of DFB is relatively low (9.0×10^{-10} mm Hg) (Wauchope and others 1992), exposures to substantial levels of DFB in air are unlikely. Thus, there have been few studies conducted on the inhalation toxicity of Dimilin. The toxicity of DFB is characterized in several reviews (Booth and others 1987, Maas and others 1980, WHO 1985, Wilcox and Coffey 1978) and in the previously developed environmental impact statement for the gypsy moth program (U.S. Department of Agriculture, Forest Service 1985 and 1989). Since the early reviews, there are only a few reports regarding the biological activities of DFB (Arafah and others 1988, el-Sebae and others 1988, Jenkins and others 1986, Perocco and others 1993) and they do not have a substantial impact on the toxicological assessment of the compound.

The available data suggest that hematological effects, reproductive effects, and cancer resulting from exposure to DFB or its metabolites are issues of potential concern for workers and the general public. DFB is known to affect the blood. The most sensitive toxic effect appears to be the induction of methemoglobin and sulfhemoglobin, modified forms of hemoglobin which are unable to function normally in the transport of oxygen.

Concern regarding the potential for reproductive effects after exposure to DFB is based on a study by Smalley (1976) in which a dose-related decrease in testosterone was observed in chickens fed DFB for 13 weeks. In addition, DFB is structurally similar to compounds that have hormonal activity, and the potential effects of insecticides and other xenobiotics on reproduction are of concern to the general public (Begley and Glick 1994). Based on a review of all of the available studies on reproductive effects, the report by Smalley (1976) appears to be an unsupported aberration. Moreover, an analysis of the structure-activity relationships for compounds similar to DFB indicates that DFB does not have the structural elements indicative of hormonal activity.

DFB has been tested for carcinogenicity in two animal species. In both assays, no carcinogenic effects were observed. A metabolite of DFB, 4-chloroaniline, has limited carcinogenic activity.

Because DFB interferes with chitin synthesis in insects, potential effects on analogous processes (for example, interference with the synthesis of connective tissue) in vertebrates are also of potential concern; however, studies have found no evidence of these effects.

6.2.2. Commercial Formulations: Impurities and Inerts

Dimilin 25W is a wettable powder containing 25% DFB by weight (Uniroyal 1991a); Dimilin 4L is a liquid containing 40.4% DFB by weight (4 pounds DFB/gallon or 479 g/L). The DFB is present as fine particulates (2–3 μ). Only small amounts of DFB are dissolved in the solution (Uniroyal 1991b). The water solubility of DFB is approximately 0.1 mg/L (Duphar 1992). Thus, 0.1 mg/L is the plausible upper limit for the amount of DFB in solution.

The commercial formulation of Dimilin 4L contains relatively small quantities of an anti-freeze and a paraffin based carrier. In addition, Dimilin contains small amounts of other benzoylphenylurea insecticides. The exact composition of these other compounds have not been chemically characterized (Dynamac 1984).

All of the toxicity studies summarized in this risk assessment involved technical grade DFB rather than the pure compound. Thus, the dose-response assessment and subsequent risk characterization is not compromised by the lack of specific data on these compounds.

6.2.3. Metabolism and Kinetics

The metabolism of DFB has been characterized in chickens and several mammalian species. As illustrated in Figure 6-1, scission (breaking or cleaving) of the carbon-nitrogen bridge is the predominant pathway in sheep, swine, and chickens. The structure and names for most scission products of DFB in mammals as well as other organisms are given in Figure 6-2.

In rats and cows, hydroxylation of either aromatic ring followed by biliary elimination is the more common pathway (WHO 1985). Hydroxylation of the aromatic ring involves the addition of a hydrogen-oxygen or hydroxy (-OH) group to one of the rings. Hydroxylation increases the water solubility of aromatic compounds. Particularly when followed by conjugation with other water soluble compounds in the body, such as sugars or amino acids, hydroxylation greatly facilitates the elimination of the compound in the urine or bile. Details of this process are given in most basic texts on pharmacology (for example, Goldstein and others 1974). All of the studies summarized in this section involved the use of ^{14}C-labelled DFB. To simplify the discussion, percent dose and percent radioactivity excreted are used synonymously.

In rats given single oral doses of DFB ranging from 4 to 900 mg/kg, intestinal absorption (measured as the total of urinary and biliary excretion) was inversely proportional to dose, decreasing from approximately 50% at 4 mg/kg to 4% at 900 mg/kg. Excretion was essentially complete after 3 days. Approximately 80% of the metabolites were conjugates of DFB hydroxylated in either aromatic ring. The remaining DFB resulted in the formation of 2,6-difluorobenzoic acid, through cleavage of the carbon-nitrogen bridge. Neither 4-chlorophenylurea nor 4-chloroaniline was detected (Williams and others 1980).

In a study in which the investigators administered 5 mg/kg DFB in a gelatin capsule to a pig and monitored elimination in the urine and feces for 11 days, approximately 80% of the dose was recovered unchanged in the feces (Opdycke and others 1982a). Urinary metabolites consisted of breakdown products of the carbon-nitrogen bridge, including 4-chloroaniline (1.03% of the total dose). Residues, measured as total radioactivity, at the end of the study were highest in the gallbladder, fat, and liver (0.2–0.43 ppm). Residues in muscle tissue were extremely low (0.04–0.05 ppm).

In black sexlinked cross chickens fed 10 ppm (approximately 0.6 mg/kg body weight/day) DFB for 63 days, residues in body fat were 1.17 ppm and residues in liver were 0.12 ppm (Miller and others 1976). Using the same treatment regimen, these investigators determined that exposure resulted in body fat residues of 1.85 ppm and liver residues of 0.45 ppm in White Leghorn chickens. DFB was not detected in muscle tissue. In a study in which the investigators administered single doses of 5 mg/kg DFB in gelatin capsules to White Leghorn and Rhode Island red chickens and monitored elimination in the feces and eggs for 13 days, approximately 90% of the dose was recovered in the feces (Opdycke and others 1982b). Approximately 50% of the elimination occurred in the first 8 hours after administration, most as unmetabolized DFB. About 0.4%–0.8% of the administered dose was eliminated in eggs. Tissue levels were highest in the kidney and ovary, ranging from approximately 0.1 to 0.2 ppm. Tissue residues in fat were low (0.01–0.04 ppm). Metabolites included 4-chloroaniline (0.44%–0.58% of the total radioactivity).

The difference between the DFB levels in fat in the two studies (Miller and others 1976, Opdycke and others 1982b) probably reflects the difference in the duration of exposure. Longer durations of exposure will increase the storage of lipophilic (fat soluble) compounds in fatty tissue.

A subsequent study demonstrates that the differences in tissue residues between the two strains of chickens were related to differences in the apparent volume of distribution of the peripheral compartment of a 2-compartment model (Opdycke and Menzer 1984). The kinetic analyses presented by these investigators is based on the work of Withey (1978).

A summary of studies regarding the metabolism of DFB in cows and sheep indicates that cows eliminated approximately 85% of a single oral dose (10–500 mg/kg) in the feces within 4 days of treatment, while sheep eliminated approximately 35% in bile, 24% in urine, and 36% in the feces (Ivie 1977). 4-Chloroaniline was not detected. Urinary metabolites were primarily scission products with some hydroxylated DFB. Biliary metabolites were primarily hydroxylated DFB. Unmetabolized DFB was the major compound identified in the feces.

Although the available data suggest that DFB is absorbed readily from the gastrointestinal tract, at least at low doses, dermal absorption is less well characterized. An unpublished study in which DFB, in an aqueous microsuspension, was applied to the shaved skin of rabbits for 6 hours indicates that after 48 hours, only 0.2% of the applied radioactivity was detected in the urine and no radioactivity was detected in the feces (Keet 1983). Similar

results were obtained in experiments using cows (Ivie 1978). Regardless of the formulation, wettable powder or oil-based solution, the investigator was unable to detect any evidence of dermal absorption over observation periods of up to 4 weeks. In one experiment, 2.1% of the applied dose was detected in the feces, but the finding was attributed to accidental contamination.

6.2.4. Effects on the Blood

As discussed in section 6.4 on dose-response assessment, the RfD for DFB is based on hematological effects (that is, effects on the blood). The effect of concern is the induction of methemoglobinemia and sulfhemoglobinemia, which are defined below.

Methemoglobin induction involves the chemical oxidation of the heme iron in hemoglobin from the ferrous (Hb^{++}) to the ferric state ($MetHb^{+++}$), resulting in the inability of hemoglobin to combine reversibly with oxygen (Smith 1980). Heme group oxidation occurs spontaneously and accounts for approximately 2% of the hemoglobin in normal individuals. Methemoglobin is reduced (restored to its natural state) by a set of enzymes referred to as **methemoglobin reductases**. The most common methemoglobin reductase is dependent on NADH, a molecule that is common in all living systems and is necessary for the proper function of many enzymes. Some individuals are deficient in NADH-dependent methemoglobin reductase, in which case as much as 50% of their blood pigment may exist as methemoglobin. Newborns are also deficient in NADH-methemoglobin reductase. Aromatic amines are known to induce methemoglobinemia, most likely by the formation of N-hydroxy metabolites. Although metabolites of this kind have not been identified for DFB, they are plausible intermediates. One known metabolite of DFB, 4-chloroaniline, has been shown to induce methemoglobinemia (McLean and others 1969, U.S. EPA 1987b).

Sulfhemoglobinemia is characterized by the presence of abnormal pigments, other than methemoglobin, in red cells and can be regarded as a form of nonspecific oxidative damage (Smith 1980). As with methemoglobinemia, sulfhemoglobinemia can be induced by aromatic amines and hydroxyamines. Unlike methemoglobinemia, sulfhemoglobinemia is irreversible. Sulfhemoglobinemia is associated with the formation of Heinz bodies, dark-staining granules found in red blood cells. The formation of Heinz bodies can lead to red cell dysfunction and hemolysis (breakdown of the cell membrane). The damaged cells are in turn captured by the spleen, which can lead to spleen enlargement. In general, cats, mice, dogs, and humans are more susceptible to Heinz body formation compared with rabbits, monkeys, chickens, and guinea pigs (Smith 1980).

Studies that demonstrate the effects of DFB on methemoglobin, sulfhemoglobin, Heinz body formation, and the spleen are summarized in Table 6-1. These data are discussed in further detail in section 6.4 on dose-response assessment.

6.2.5. Carcinogenicity

The carcinogenicity of DFB has been tested in rats and mice. No carcinogenic effects were observed in rats exposed to DFB in a 2-year feeding study (Keet 1984a). Neither treated nor control rats had cancers of any type, although pathology changes were observed in the spleen of both male and female rats. In mice, no carcinogenic effects or changes in spleen pathology were observed in males or females in a 2-year feeding study (Keet 1984b). Details of these and other studies are summarized in Table 6-1.

In addition to its lack of carcinogenic activity in in vivo bioassays, DFB has produced negative results in several bioassays for mutagenicity or other damage to DNA. Negative findings include a dominant lethal study in mice (Arnold 1974), cell transformation assays using BALB/3T3 cells (Brusick and Weir 1977a), the induction of unscheduled DNA synthesis (Brusick and Weir 1977b), transplacental transformation assays using hamster cells (Quarles and others 1980), Ames assays using various strains of Salmonella typhimurium with and without metabolic activation (Brusick and Weir 1977c, Bryant 1976, McGregor and others 1979, Seuferer and others 1979), and a Drosophila wing mosaic assay (Szabad and Bennettovia 1986).

There are two studies that suggest that DFB may have limited mutagenic potential. In one of those studies, DFB induced cell transformations in BALB/c 3T3 cells in the absence of metabolic activation; however, the effect was not observed with metabolic activation (Perocco and others 1993). Furthermore, the potency of DFB in this assay was substantially less than that of either 3-methylcholanthrene or B(a)P. In the other study, there was a positive relationship in cultured mouse cells between the concentration of DFB in culture media and the number of metaphase cells with aberrations (Kurinnyi and others 1982).

DFB has been shown to inhibit the uptake of uridine, adenosine, and cytidine in cultured melanoma cells (Mayer and others 1984) and inhibit the in vivo growth of melanomas in mice (Jenkins and others 1986). Since the inhibition was enhanced by mixed function oxidase induction with 3-methylcholanthrene or beta-napthaflavone, aromatic hydroxylation was suggested as a requisite to tumor inhibition.

The weight of evidence for DFB clearly does not suggest a high potential for carcinogenic effects based on the available carcinogenicity and mutagenicity studies using DFB. These data have not been formally evaluated by IARC (1982) or the U.S. EPA (1987a). Using the U.S. EPA (1987a) classification, DFB could be classified as **Group E -- Evidence of Non-Carcinogenicity**. As defined by U.S. EPA (1987a), this classification indicates: "... no evidence for carcinogenicity in at least two adequate animal tests in different species ...".

There is experimental evidence that 4-chloroaniline, a known metabolite of DFB, has mutagenic potential (Prasad 1970) and may be carcinogenic to male rats (NCI 1979). In the cancer study, groups of 50 male and 50 female Fischer 344 rats and groups of B6C3F1 mice were exposed to dietary concentrations of 4-chloroaniline for 78 weeks. The exposure

concentrations were 250 and 500 ppm for rats and 2,500 and 5,000 ppm for mice. Male rats in the high dose group had an increased incidence of rare splenic neoplasms [that is, cancers of the spleen including fibroma, fibrosarcoma, sarcoma (not otherwise specified), hemangiosarcoma, and osteosarcoma]. The tumor incidence was 0/20 in the control group, 0/49 in the low dose group, and 10/49 in the high dose group. In mice, there was a weak association between exposure and the induction of tumors. The dose-response relationship in rats is significant at $p=0.001$. Including one metastatic sarcoma observed in the control group, the dose-response relationship is not statistically significant ($p=0.106$). Nonetheless, these tumors are rare in the Fischer rat. Using historical controls (1/360), the relationship is statistically significant. Overall, the study concluded that these results indicate carcinogenic activity in male rats. As with DFB, 4-chloroaniline has not been evaluated by IARC or the U.S. EPA. Using the U.S. EPA (1987a) ranking scheme for carcinogenicity, 4-chloroaniline would be ranked as a **Group C: Possible Human Carcinogen** because there are no studies on the carcinogenicity of 4-chloroaniline in humans and a positive carcinogenic response has been observed in only one species.

For the current risk assessment, cancer risk will be quantified for both DFB and 4-chloroaniline, as discussed in the dose-response assessment (section 6.4). Evaluating the potential for carcinogenic effects after exposure to DFB must take into consideration two exposure factors. First, as discussed in the exposure assessment (section 6.3), 4-chloroaniline can form in the environment through the degradation of DFB, and 4-chloroaniline is known to be potentially carcinogenic. Second, exposure to DFB may result in the metabolism of DFB to 4-chloroaniline in humans, which may involve the risk of carcinogenic effects. To the extent that levels of 4-chloroaniline in environmental media can be quantified, information regarding the carcinogenic potency of the compound can be used to assess risk. That direct exposure to DFB presents a similar risk through the metabolic formation of 4-chloroaniline is less clear, although nonetheless plausible. Both DFB and 4-chloroaniline induce a similar spectrum of toxic effects in the blood and spleen, and the known carcinogenic effect of 4-chloroaniline is on the spleen. Concern for the potential carcinogenicity of DFB is enhanced by the limited information indicating that DFB may be weakly mutagenic.

6.2.6. Reproductive Effects

Certain insecticides, such as DDT (Bustos and others 1988), methoxychlor (Bulger and others 1985), and aldrin (Chatterjee and others 1992), as well as several other classes of chemicals (Jordan and others 1985) have been shown to be estrogenic and impair reproductive performance in mammals. Concern regarding the potential estrogenic activity of DFB is expressed in a study conducted by the USDA (Smalley 1976 p. 27). The report is brief and important enough to be quoted:

> TH-6040 [DFB] was tested in baby chicks, incorporated into the feed and fed for 13 weeks. Effects on the female chicks were greatly increased fat

deposition, so the hen weighed 6½ lb at the end, compared to 3 lb for the normal broiler, our controls, and the males. The test males, or cocks, did not appear to mature--the combs, wattles, feathers, and voice remained undeveloped through the 13-week period and were related to a dose-related decrease in testosterone.

The dose levels are not specified. This study is published only as an abstract and additional details of this study were not found in the available literature.

Other studies regarding the potential estrogenic activity of DFB, all of which were conducted by the USDA, are summarized in Table 6-2. The report by Smalley (1976) is inconsistent with the results of other investigators. This study was conducted at the Veterinary Toxicology and Entomology Research Laboratory, ARS, USDA, College Station, Texas. The Kubena (1982) full publication was conducted at the same facility but does not mention the Smalley (1976) report; neither do the other USDA publications. The only effect reported in any of the studies is decreased weight in the male progeny of 28-week-old chickens exposed to 50 ppm and increased weight in female progeny 8 weeks after birth in all dose groups (Cecil and others 1981). These changes, however, are relatively minor. The investigators did not attribute these effects to treatment. In the subchronic and chronic toxicity studies summarized previously, no effects have been noted that support concern for the estrogenic activity of DFB. In addition, several teratogenicity and multigeneration reproduction studies have been conducted in experimental mammals, in which adverse effects were not reported (WHO 1985).

A further assessment of the potential estrogenic activity of DFB can be made based on the most recently published data regarding qualitative structure-activity relationships of estrogenic compounds (Jordan and others 1985). Generally, nonsteroidal estrogenic compounds are characterized by at least two aromatic rings separated by a flexible aliphatic bond with hydroxyl substitution in both para positions on the aromatic rings. This model is illustrated in Figure 6-3, which indicates how methoxychlor becomes estrogenic via metabolism to a para-biphenolic derivative (hydroxyl groups on both aromatic rings in the carbons opposite to the bridge joining the two aromatic rings) (Bulger and others 1985). Although DFB contains two aromatic rings separated by a flexible carbon-nitrogen bridge, dehalogenation of the aromatic rings with the substitution of hydroxyl groups in the para position (the carbon opposite to the carbon-nitrogen bridge) has not been demonstrated in vertebrates.

The weight of the experimental evidence supported by qualitative structure-activity relationships suggests that DFB is not estrogenic and is not likely to cause reproductive effects. The study by Smalley (1976) is unsupported by subsequent detailed publications from the same research facility. Consequently, this endpoint will not be considered quantitatively in the risk assessment.

6.2.7. Other Effects

Because DFB interferes with macromolecular synthesis in insects, the potential for analogous effects in mammals may be a potential concern. Evidence of such effects on biomacromolecules has not been reported in the toxicology studies summarized above. In addition, effects such as these have been examined in various biochemical studies (Maas and others 1980) and no effects have been found on the synthesis of biomacromolecules in mammals or other vertebrates.

6.3. Exposure Assessment

6.3.1. Workers

6.3.1.1. Overview and Assumptions

Two general exposure assessments are presented in this section, job-specific assessments and incident assessments. Job-specific assessments estimate absorption associated with relatively complex job activities, such as mixing, loading, or applying DFB, in which multiple routes of exposure are likely. Incident assessments are relatively simple. They estimate absorption either from spilling DFB onto the skin or wearing clothing that was saturated with DFB.

There are no studies available regarding occupational exposure to DFB. Consequently, estimation methods based on worker exposure to other pesticides are used. The general form of the estimate is:

$$Dose_{Abs} = R \cdot Q \quad (14)$$

where:

$Dose_{Abs}$ = *absorbed dose (mg/kg)*

R = *absorption rate (mg/kg bw·kg ai handled)*

Q = *amount of active ingredient (ai) handled (kg)*

Data regarding estimations of job-specific absorption rates for DFB were not located in the available literature. Several studies report general relationships between the amount of 2,4-D handled per day by various workers and the amount of 2,4-D absorbed by the workers. Although occupational exposure usually involves more than one route (for example, dermal and inhalation), most studies that attempt to differentiate occupational exposure by route of exposure indicate that dermal exposure is the predominate route for pesticide workers (van Hemmen 1992a and 1992b). Thus, in applying these estimates to DFB, differences in dermal absorption rates between 2,4-D and DFB are considered. The general form of this correction is:

$$R_{DFB} = \frac{\%Abs_{DFB}}{\%Abs_{2,4\text{-}D}} \cdot R_{2,4\text{-}D} \qquad (15)$$

where:
% Abs = dermal absorption rate (% applied dose/day)

The limited experimental data regarding various formulations of DFB indicate that the compound is not well absorbed by the skin. When applied as an aqueous microsuspension to the shaved skin of rabbits for 6 hours, 0.2% of the applied dose was eliminated in the urine within 48 hours (Keet and others 1982). According to another study regarding urinary elimination of DFB after skin application, cows eliminated 15% of the absorbed dose and sheep eliminated 50% (Ivie 1978). Assuming that comparable rates for rabbits fall within this range, the estimated daily absorption rate of DFB in the Keet and others (1982) study ranges from 0.002

$$(0.2\% \div 2 \text{ days}) \div 0.5 = 0.002 \text{ day}^{-1}$$

to 0.007 day^{-1}

$$(0.2\% \div 2 \text{ days}) \div 0.15 = 0.0066 \text{ day}^{-1}.$$

Similarly, in a study involving the application of a 25W formulation, no DFB was detected in the urine of cattle over a 3-day period after exposure (Ivie 1978). Approximately 2.1% of the applied dose was recovered in the feces; however, this finding was attributed to accidental contamination. A conservative approach, which assumes that the DFB recovered in the feces was due to dermal absorption, leads to an estimated absorption rate of 0.007 day^{-1}, the upper limit of the estimate based on the rabbit study.

These estimated absorption rates are a factor of between 2 and 8 less than the estimated average absorption rate of 0.017 day^{-1} based on the relationship of absorption rate to molecular weight (Rubin and others 1994), but fall within the range of variability of the estimate. There are no data in the published literature or in studies submitted to the U.S. EPA regarding the dermal absorption of DFB from exposure to Dimilin 4L.

The absorption rate of 2,4-D in humans was measured in a study in which 5.8% of 2,4-D, applied to the ventral forearm of volunteers, was absorbed over a 5-day period (Feldmann and Maibach 1974). For DFB, the rate of 0.002 day^{-1} from the rabbit study will be used as the central or most likely estimate. Thus, for a 5-day period, it will be assumed that 1% of DFB is absorbed (0.002 day^{-1} · 5 days = 0.01). The ratio of these values (1% ÷ 5.8% = 0.17) is used in routine exposure scenarios to estimate the relative absorption of DFB with respect to 2,4-D. For extreme scenarios, a value of 3.5% (0.007 day^{-1} · 5 days) is used, and relative absorption is taken as 0.6 (3.5% ÷ 5.8%).

For scenarios requiring that the estimated absorption rate of DFB be expressed as percent of applied dose-day, the value of 0.002 day^{-1} is also used in the routine scenario. For the extreme scenario, a value of 0.007 day^{-1} is used, based on both the rabbit and cow studies.

Scenarios that use Fick's first law require an estimate of the permeability coefficient, K_p, expressed in cm per hour. There is not an experimentally determined K_p value for DFB in the available literature. Based on structure-activity relationships (U.S. EPA 1992), a K_p of 0.014 cm/hour for an aqueous solution of DFB can be calculated from the following equation:

$$\log K_p = -2.7 + 0.71 \log K_{o/w} - 0.0061\ MW \qquad (16)$$

where $K_{o/w}$ is the octanol water partition coefficient and **MW** is the molecular weight. For DFB, the molecular weight is 310.7 and the log K_{ow} is 3.88 (Duphar 1992).

For the purposes of risk assessment, exposure to saturated solutions is estimated using the aqueous K_p value and the solubility of DFB in water. This approach is taken because Dimilin 4L and aqueous preparations of Dimilin 25W are suspensions of DFB, not solutions of the compound. Although it is possible that the adjuvants in Dimilin 4L may enhance solubility, the quantities of those adjuvants in the formulation are relatively small and unlikely to affect the rate of dermal absorption. Thus, Dimilin 25W and Dimilin 4L are essentially aqueous solutions of DFB at a concentration that is limited by the water solubility of the compound.

In accidental spill scenarios, it is important to estimate the amount of liquid adhering to the surface of the skin. In one study, as much as 4 mg liquid/cm^2 of skin surface was retained on hands removed immediately from beakers containing water or ethanol (Mason and Johnson 1987). When beakers containing light paraffin oil were used, approximately twice this amount was retained. In most instances, using these values should result in a plausible upper estimate of retention because losses of the chemical from the surface of the skin due to moving or washing are not considered. Thus, the amount of chemical transferred to the skin after a spill may be calculated as:

$$D_{Skin} = RF \cdot P \cdot A \qquad (17)$$

where:

D_{Skin} = *dose remaining on surface of skin* (μg)

RF = *retention factor* ($\mu g/cm^2$) (*for example*, 4,000–8,000 $\mu g/cm^2$)

P = *proportion of DFB in the liquid*

A = *skin area exposed* (cm^2)

6.3.1.2. Aerial Applications

The most complete data concerning the aerial application of pesticides and worker exposure are available for 2,4-D. The absorption rate for 2,4-D, expressed as mg/kg body weight/day absorbed dose-kg ai handled, for mixer/loaders and pilots is estimated at $2 \cdot 10^{-5}$, with an empirical range of $3 \cdot 10^{-6}$ to $3 \cdot 10^{-4}$. For flagmen, the corresponding absorption rate is $3 \cdot 10^{-7}$ with a range of $4 \cdot 10^{-8}$ to $4 \cdot 10^{-6}$ (Lavy and others 1982).

The amount of DFB handled per day by workers applying Dimilin from aircraft can be calculated from application rates and the number of acres treated each day. Based on information received from regional gypsy moth program managers (Kirchenbauer 1994, Largen 1994), 2,000 acres are usually treated with Dimilin during a single day of aerial applications. An empirical upper limit for this value is approximately 12,000 acres. Each day, application involves two or three flight crews and one ground crew. Using the absorption rates and areas treated, and assuming a maximum application rate of 28 g/acre, absorbed doses can be estimated for pilots, mixer/loaders, and flagmen.

For the mixer/loaders, the typical absorbed dose is estimated at $1.9 \cdot 10^{-4}$ mg/kg

$$2 \cdot 10^{-5} \text{ mg/kg/day/kg ai} \cdot (1\% \div 5.8\%) \cdot 0.028 \text{ kg ai/acre} \cdot 2{,}000 \text{ acres/day} \cdot 1 \text{ day} = 1.9 \cdot 10^{-4} \text{ mg/kg.}$$

The upper limit for mixer/loaders based on the number of acres treated and using the upper limit on the dermal absorption of DFB is $6.1 \cdot 10^{-2}$ mg/kg

$$3 \cdot 10^{-4} \text{ mg/kg/day/kg ai} \cdot (3.5\% \div 5.8\%) \cdot 0.028 \text{ kg ai/acre} \cdot 12{,}000 \text{ acres/day} = 6.1 \cdot 10^{-2} \text{ mg/kg.}$$

For pilots, the estimates are one-half of those for mixer/loaders, because at least two air crews are used each day during application.

The typical absorbed dose for flagmen is estimated at $2.9 \cdot 10^{-6}$ mg/kg

$$3 \cdot 10^{-7} \text{ mg/kg/day/kg ai} \cdot (1\% \div 5.8\%) \cdot 0.028 \text{ kg ai/acre} \cdot 2{,}000/\text{day acres} = 2.9 \cdot 10^{-6} \text{ mg/kg.}$$

The upper limit for flagmen based on the number of acres treated and using the upper limit on the dermal absorption of DFB is $8.1 \cdot 10^{-4}$ mg/kg

$$4 \cdot 10^{-6} \text{ mg/kg/day/kg ai} \cdot (3.5\% \div 5.8\%) \cdot 0.028 \text{ kg ai/acre} \cdot 12{,}000 \text{ acres/day} = 8.1 \cdot 10^{-4} \text{ mg/kg.}$$

6.3.1.3. Ground Applications

There is tremendous variation in the apparent levels of absorbed dose associated with different methods of ground application. The most highly exposed individuals seem to be those involved in backpack applications. Based on one study (Lavy and others 1982), an absorption rate for backpack sprayers applying 2,4-D can be calculated at $7 \cdot 10^{-2}$ mg/kg/day/kg ai with a range of $2 \cdot 10^{-2}$ to $2 \cdot 10^{-1}$ mg/kg/day/kg ai. According to the APHIS database on the use of gypsy moth control agents, the average size of a plot treated with Dimilin is 3.8 acres and the largest plot treated is 15 acres. For this risk assessment, the conservative assumption will be made that each plot is treated by only one worker. For ground workers, the estimated absorbed dose for a routine exposure is $1.3 \cdot 10^{-3}$ mg/kg

$$7 \cdot 10^{-2} \text{ mg/kg/day/kg ai} \cdot (1\% \div 5.8\%) \cdot 0.028 \text{ kg ai/acre} \cdot 3.8 \text{ acres/day} \cdot 1 \text{ day} = 1.3 \cdot 10^{-3} \text{ mg/kg.}$$

For the extreme scenario, using the upper limit on the number of acres treated and the dermal absorption of DFB, the estimated absorbed dose for a routine exposure is $5.1 \cdot 10^{-2}$ mg/kg

$$2 \cdot 10^{-1} \text{ mg/kg/day/kg ai} \cdot (3.5\% \div 5.8\%) \cdot 0.028 \text{ kg ai/acre} \cdot 15 \text{ acres/day} \cdot 1 \text{ day} = 5.1 \cdot 10^{-2} \text{ mg/kg.}$$

6.3.1.4. Immersion or Saturated Clothing

During the handling process, an individual may accidentally immerse a part of the body into the insecticide formulation for a short time. One scenario might be a worker who places both hands (0.084 m^2) in Dimilin 4L for 1 minute. For such an exposure, Fick's first law can be applied (U.S. EPA 1992). Although the nominal level of DFB in Dimilin is approximately 479 mg/mL, most of the DFB is present as particulates, which will not be well absorbed. For the application of Fick's first law, the solution in contact with the skin will be treated as a saturated aqueous solution. The solubility of DFB in water is approximately 0.1 mg/L (Duphar 1992). A concentration of 0.1 mg/L is equivalent to 0.0001 mg/mL or 0.0001 mg/cm^3. Thus, the estimated absorbed dose, using Fick's first law, is approximately $2.8 \cdot 10^{-7}$ mg/kg

$$0.014 \text{ cm/hour} \cdot 0.0001 \text{ mg/cm}^3 \cdot 1/60 \text{ hour} \cdot 840 \text{ cm}^2 \div 70 \text{ kg.}$$

Estimated doses for other immersed areas and durations can be calculated in a similar way. If, however, the scenario involves saturated clothing (for example, gloves), which might be worn for a long time, absorbed doses could be much higher. For example, contaminated gloves worn for 1 hour would lead to an exposure 60 times greater than that described for the immersion scenario (that is, $1.7 \cdot 10^{-5}$ mg/kg).

6.3.1.5. Accidental Spill

Any person handling concentrated Dimilin or located near the area where the handling takes place may be subject to an accidental spill. This is different from immersion in that most of the liquid will run off the surface of the skin immediately after the spill unless the material is kept in contact with the skin by saturated clothing. If the clothing is saturated, the scenario outlined above applies. If the material spills onto the skin and is not kept in contact with the skin, the exposure will be much less.

Consider the effects of spilling Dimilin over the lower legs. The surface area of the lower legs is taken as 2,070 cm^2 (U.S. EPA 1992). The upper limit of the amount of liquid adhering to the surface of the skin is taken as 8 mg/cm^2 of skin (Mason and Johnson 1987). Assuming a density of 1.0 for the aqueous solution, this is equivalent to 0.008 mL/cm^2. Hence, the volume of liquid adhering to the skin is 16.56 mL (2,070 cm^2 · 0.008 mL/cm^2). The amount of Dimilin adhering to the skin can be estimated as 7,932 mg (16.56 mL · 479 mg/mL). Assuming that the skin is washed thoroughly after 1 hour and using the typical absorption rate (0.002 day^{-1}), the absorbed dose can be estimated as 0.009 mg/kg

$$7{,}932 \text{ mg} \cdot 0.002 \text{ day}^{-1} \cdot (1 \text{ hour} \div 24 \text{ hours}) \cdot 1 \text{ hour} \div 70 \text{ kg} = 0.009 \text{ mg/kg}.$$

For an extreme scenario, it can be assumed that the individual does not wash the skin for 24 hours and the upper limit on the absorption rate (0.007 day^{-1}) can be used. In this case, the absorbed dose is calculated as 0.79 mg/kg

$$7{,}932 \text{ mg} \cdot 0.007 \text{ day}^{-1} \cdot 1 \text{ day} \div 70 \text{ kg} = 0.79 \text{ mg/kg}.$$

6.3.2. General Public

6.3.2.1. Scenarios and Assumptions

Any number of exposure scenarios could be constructed for the general public, based on varying assumptions concerning application rates, dispersion, canopy interception, and human activity. For this risk assessment, conservative assumptions will be applied, as in the worker scenarios. Specifically, no canopy interception will be assumed and maximum application rates will be used.

Many of the exposure scenarios for the general public involve a child. This is because the relationships of surface area and consumption rates to body weight result in estimated doses (mg agent/kg body weight) for young children that are higher than those for adults (U.S. EPA 1987c). Consumption-specific values are taken from U.S. EPA (1989a). Values used only once are discussed below. Dermal exposure scenarios that involve children use the same set of assumptions: the child is 2 to 3 years old, weighs 11 kg, and has a total body

surface area of 0.6 m^2 or 6,000 cm^2 (U.S. EPA 1992). For most scenarios, the child is assumed to be naked, maximizing the surface area of the body in contact with the chemical. In all cases, there are linear relationships among the exposed surface area of the body, the estimated absorbed dose, and the subsequent risk. The chemical-specific assumptions for DFB are the same as those used for workers.

6.3.2.2. Direct Spray

For this exposure scenario, it will be assumed that a naked child is sprayed directly with Dimilin during an aerial application. Assuming that the child is in a prone position (that is, 50% of the surface area of the body is exposed) and that the application rate is 28 g/acre (approximately 7 mg/m^2), the dose deposited on the child will be 2.1 mg

$$50\% \cdot 0.6\ m^2 \cdot 7\ mg/m^2 = 2.1\ mg.$$

Taking the average absorption rate of 0.002 day^{-1} and assuming that the child is washed completely 1 hour after being sprayed, the absorbed dose is estimated as $1.6 \cdot 10^{-5}$ mg/kg

$$2.1\ mg \cdot 0.002\ day^{-1} \cdot (1\ hour \div 24\ hours) \div 11\ kg = 1.6 \cdot 10^{-5}\ mg/kg.$$

An extreme scenario may be based on the upper limit of the absorption rate, 0.007 day^{-1}, and the assumption that the child is not washed effectively, therefore, exposure continues for the entire day. In this case, the absorbed dose is estimated at $1.3 \cdot 10^{-3}$ mg/kg

$$2.1\ mg \cdot 0.007\ day^{-1} \div 11\ kg = 1.3 \cdot 10^{-3}\ mg/kg.$$

6.3.2.3. Emergency Ejection of Spray Load

For this exposure scenario, it will be assumed that a child is saturated with Dimilin as a result of the pilot having to eject the entire load of DFB in an emergency situation (for example, power loss). Dimilin 4L contains 479 mg/mL of DFB. In aerial sprays, this is diluted so that 0.5–1 gallon of material is sprayed over each acre. Thus, at the maximum application rate of 28 g/acre and the minimum dilution volume of 0.5 gallons/acre, the amount of DFB in the sprayed material is 15 mg/mL (that is, 28 g/gallon is approximately 7.5 mg/mL and 28 g/half gallon is approximately 15 mg/mL).

As with the worker scenarios, 0.008 mL/cm^2 is used as the amount of liquid retained on the surface of the skin; in which case, the amount of DFB adhering to the skin surface is 720 mg

$$15\ mg/mL \cdot 6{,}000\ cm^2 \cdot 0.008\ mL/cm^2 = 720\ mg.$$

Using the typical absorption rate of 0.002 day^{-1} and assuming that the child is washed thoroughly after 1 hour, the absorbed dose is estimated as 0.0055 mg/kg

$$720 \text{ mg} \cdot 0.002 \text{ day}^{-1} \cdot (1 \text{ hour} \div 24 \text{ hours}) \div 11 \text{ kg} = 0.0055 \text{ mg/kg}.$$

If an absorption rate of 0.007 day^{-1} were used, the absorbed dose would be 0.02 mg/kg

$$720 \text{ mg} \cdot 0.007 \text{ day}^{-1} \cdot (1 \div 24) \div 11 \text{ kg} = 0.02 \text{ mg/kg}.$$

Because of the extreme nature of this scenario, it is not reasonable to assume that the child would remain unwashed for a longer period of time.

This scenario can be modified by assuming that the clothing of a child is saturated with the ejected DFB. For this scenario, Fick's first law could be used to estimate absorption. Using the K_p of 0.014 cm/hour and assuming that half of the body surface is in contact with saturated clothing for 1 hour, the absorbed dose is estimated as $3.8 \cdot 10^{-4}$ mg/kg

$$0.014 \text{ cm/hour} \cdot 0.0001 \text{ mg/mL} \cdot 6{,}000 \text{ cm}^2 \cdot 50\% \cdot 1 \text{ hour} \div 11 \text{ kg} = 3.8 \cdot 10^{-4} \text{ mg/kg}.$$

6.3.2.4. Dermal Exposure from Contaminated Vegetation

In this exposure scenario, it is assumed that Dimilin is sprayed at the maximum application rate of 28 g/acre and that a naked child is in contact with sprayed vegetation or other contaminated surfaces (for example, lawn furniture) immediately after the spray operation. Cameron and others (1985) studied the transfer of DFB from contaminated surfaces after the aerial application of DFB at a rate of 14 g ai/acre. Transfer was estimated based on levels of DFB on monitoring pads attached to various sites on volunteers. Average residues on the 103.2 cm^2 pads after 1 hour of normal activity immediately after spraying were 6.8 μg/pad or 0.07 $\mu g/cm^2$. Assuming a linear relationship between application rate and dermal transfer, an application rate of 28 g ai/acre would be associated with a transfer rate of 0.14 $\mu g/cm^2$. Assuming that a child is in contact with the vegetation for 8 hours, the amount deposited on the surface of the skin would be approximately 6.7 mg

$$0.14 \ \mu g/(cm^2 \cdot \text{hour}) \cdot 8 \text{ hours} \cdot 6{,}000 \text{ cm}^2 = 6{,}720 \ \mu g \approx 6.7 \text{ mg}.$$

Assuming that absorption proceeds for 24 hours (that is, the child is not washed thoroughly), the estimated absorbed dose is 0.0043 mg/kg

$$6.7 \text{ mg} \cdot 0.007 \text{ day}^{-1} \div 11 \text{ kg} = 0.0043 \text{ mg/kg}.$$

Cameron and others (1985) also measured transfer rates 1 week after spraying. Most measurements indicated no detectable levels of DFB. From skin pad measurements, which

did detect levels of DFB, a transfer rate of 0.002 $\mu g/cm^2 \cdot hour$ can be calculated. If this value is used with the same assumptions outlined in the previous paragraph, the absorbed dose can be calculated as 0.061 $\mu g/kg$

$$0.002\ \mu g/(cm^2 \cdot hour) \cdot 6{,}000\ cm^2 \cdot 8\ hour \cdot 0.007\ day^{-1} \div 11\ kg = 0.061\ \mu g/kg.$$

Two weeks after spraying, the investigators were unable to detect residue levels on individuals involved in various activities in the spray area (Cameron and others 1985).

6.3.2.5. Contaminated Water

Water can be contaminated from runoff or from direct spray. There are several monitoring studies regarding DFB levels in water after aerial or ground applications of the compound. The most relevant studies are summarized in Table 6-3. These studies suggest that if DFB were applied at rates comparable to the highest rate recommended to control the gypsy moth, levels of the compound in surface water or runoff would be approximately 1–10 $\mu g/L$ immediately after spraying.

Data are available regarding monitored levels of DFB and p-chlorophenylurea in surface water samples from pastures and dairy drains after these areas were treated with DFB to control mosquitos (Schaefer and Dupras 1976). Three formulations were used, WP-25 (25% wettable powder) usually applied by aircraft, a liquid applied by hand or power sprayers, and a granular formulation applied from aircraft. Replicate samples were taken 1 hour, 1 day, 2 days, and 3 days after treatment. As indicated in Table 6-3, application rates ranged from 9 to 50 g/acre. Aerial applications of wettable powder and granules generally resulted in comparable levels of DFB in water, although there seems to have been substantial variability. Levels of DFB after 1 hour at high application rates (greater than 30 g/acre) are much greater for most liquid formulations but decrease to levels comparable to those resulting from lower applications of wettable powders after 24 hours. It is not clear whether the differences in initial levels are due to the different application methods (ground versus aerial) or the different formulations or perhaps both. According to the investigators, the scatter in the data is due somewhat to site-specific differences in the amount of organic debris present at each site.

An analysis of the data provided by Schaefer and Dupras (1976) provides simple half-times of approximately 0.7 days for the applications using wettable powder, 0.2 days for the liquids, and 1.5 days for the granules. These estimates, however, are misleading; visual inspection of the data and statistical analyses suggest that a simple first order decay model is inappropriate. The general pattern indicates a rapid initial decrease in concentration, probably related to dispersion and sorption, followed by a slower decrease that may be related either to further dispersion processes or conversion to environmental metabolites or both.

Data regarding levels of DFB in surface waters were located in the available literature. Dimilin 25W was applied from an aircraft at a rate of 28 g/acre, and levels of DFB were monitored in two ponds and two streams that received direct spray (Sundaram and others 1991). Detectable levels of DFB were not found in the ponds after 15 days or in the streams after 1 day. Levels in the two ponds during the first 15 days after application are illustrated in Figure 6-4. These investigators report DFB half-times of 0.4 days in Pond 1 and 1.3 days in Pond 2. The half-time for DFB based on the combined data for both ponds is approximately 2.7 days. Although the simple exponential decay model adequately fits the data ($p=0.00019$), the kinetics of DFB loss appear to be more complex than first order. This is particularly evident for Pond 1.

In the streams, DFB levels were substantially lower than those in the ponds (Table 6-3) (Sundaram and others 1991). Levels of the compound in streams may be particularly variable depending on differences in terrain, flow-rate, and weather (Jones and Kochenderfer 1988). In this study, DFB was applied to an area at a rate of 27 g/acre. After 1 hour, the level of DFB was 0.11 μg/L; after 1.5 hours and a 0.5 inch rain, the level was 2.1 μg/L.

Levels of DFB in runoff water and groundwater after the aerial application of 30 g/acre Dimilin 25W are reported by Mutanen and others (1988). Runoff water was sampled by digging a 2 x 2 m pit 0.5 m deep in a pine swamp. Groundwater was sampled by digging a shaft 0.6 m in diameter and 3 m deep in a mineral soil pit. The concentration of DFB in the runoff water 1 day after application was 5 μg/L, similar to the levels reported in surface water (Schaefer and Dupras 1976, Sundaram and others 1991). The rate of disappearance from runoff water was much slower (half-time = approximately 58 days) than that reported for surface water. As with the other kinetic patterns, a simple first order decay model does not seem appropriate for these data. Neither 4-chloroaniline nor 4-chlorophenylurea were detected (limit of detection = 0.2 μg/L). Detectable levels of DFB may be present in surface waters for up to 10 months after application (Fischer and Lenwood 1992).

These monitoring studies suggest that when Dimilin is applied at the maximum application rate, DFB levels in runoff water and surface water are generally 10 μg/L or less. Consequently, for a 10 kg child who consumes 1 L of water each day, the resulting dose is 0.001 mg/kg

$$10\ \mu g/L \cdot 1\ L \div 10\ kg = 1\ \mu g/kg.$$

These studies also suggest that DFB levels in water will decrease to approximately 1 μg/L after 2 weeks or so. The levels of 4-chloroaniline are likely to be about 10% of those of DFB (Schaefer and others 1980).

A more conservative exposure scenario involves the child consuming 0.5 L of water immediately after the surface water receives a direct spray. An application rate of 28 g/acre is approximately 7 mg/m^2

$$28 \text{ g/acre} \div 4{,}047 \text{ m}^2\text{/acre} = 0.0069 \text{ g/m}^2 \simeq 7 \text{ mg/m}^2.$$

Assuming a shallow mixing depth of 10 cm (0.1 m or about 4 inches), the concentration in the water would be 0.07 mg/L

$$7 \text{ mg/m}^2 \div (0.1 \text{ m} \cdot 1{,}000 \text{ L/m}^3) = 70 \text{ mg/m}^3 = 0.07 \text{ mg/L}.$$

The oral dose would be 0.004 mg/kg

$$0.07 \text{ mg/L} \cdot 0.5 \text{ L} \div 10 \text{ kg} = 0.0035 \text{ mg/kg}.$$

6.3.2.6. Contaminated Fish

In this exposure scenario, it is assumed that individuals consume fish from a pond after an aerial spray with Dimilin. Estimated amounts of ingested chemical, either DFB or 4-chloroaniline, are based on estimated levels of these compounds in ambient water, estimations of the bioconcentration factor (BCF) for these compounds, and estimated amounts of fish consumption. The BCF is defined as the level in fish (mg/kg) divided by the level in water (mg/L).

The most directly relevant data on the bioconcentration of DFB and 4-chloroaniline comes from the study in which DFB was added to pond water (Schaefer and others 1980). Residues of DFB and 4-chloroaniline were determined in water and fish during a 19-day period (Table 6-4). Water levels were comparable to those monitored after the application of DFB for gypsy moth control. BCF values for DFB ranged from approximately 50 to 100. Substantially lower values (4–10), were reported for 4-chloroaniline.

In a model ecosystem, DFB was concentrated by a factor of 80 by the fish Gambusia affinis. Only small quantities of 4-chloroaniline (0.44%–0.7%) were detected in soil (Metcalf and others 1975). In a static assay conducted over 24 hours, the bioconcentration of DFB in bluegills ranged from 14 to 20 (Schaefer and others 1979). 4-Chloroaniline levels were not determined.

The upper limit of fish consumption, 0.14 kg/day, will be used to represent the amount of contaminated fish consumed each day (U.S. EPA 1989d). Based on the study by Schaefer and others (1980), the BCF for DFB will be taken as 100. The BCF for 4-chloroaniline will be taken as 10. These are the upper limits of the measured BCF values and lead to a conservative but plausible exposure assessment.

Levels in water are likely to vary depending on a number of environmental conditions that cannot be modeled with precision. For this risk assessment, a semi-quantitative approach is taken. The maximum monitored levels in water just after spraying takes place are

approximately 10 μg/L. After 2 weeks and for period of up to 30 days after treatment, the levels drop to approximately 1 μg/L. Over the longer term, water levels have been reported to stabilize at approximately 0.1 μg/L. For the exposure assessment, it will be assumed that 0.1 μg/L DFB is found in the water for a period of 30 days to 10 months after treatment. For months 11 and 12 after treatment, water levels of DFB will be assumed to be 0.

Based on the above assumptions, initial doses of DFB resulting from the consumption of contaminated fish would be about $2 \cdot 10^{-3}$ mg/kg/day

$$0.14 \text{ kg/day} \cdot 0.01 \text{ mg/L} \cdot 100 \text{ L/kg} \div 70 \text{ kg} = 2 \cdot 10^{-3} \text{ mg/kg/day}.$$

The corresponding dose for 4-chloroaniline would be $2 \cdot 10^{-4}$ mg/kg/day

$$0.14 \text{ kg/day} \cdot 0.01 \text{ mg/L} \cdot 10 \text{ L/kg} \div 70 \text{ kg} = 2 \cdot 10^{-4} \text{ mg/kg/day}.$$

The risk assessment scenarios involving long-term exposure are based on the assumption that these levels will decrease, as discussed above.

6.3.2.7. Consumption of Contaminated Vegetation

In this exposure scenario, it is assumed that individuals consume vegetation after an aerial spray of Dimilin at the maximum application rate. Since most spraying is done in early spring before most crops emerge, the practical significance of this scenario may be limited.

Data are available regarding DFB levels on vegetation after application of the compound to control the gypsy moth (Carr and others 1991). These investigators have summarized monitoring studies performed during the 1989 and 1990 Gypsy Moth Eradication Project conducted in Martin and Placier counties, California. During the project, Dimilin 25W was applied by ground spray rigs at application rates of 0.2–0.4 ounces ai/acre. Maximum residues on foliage occurred immediately after the second application and were 18.31 μg/g (w/w) or 0.252 $\mu g/cm^2$ (surface area).

Martinat and others (1987) monitored the levels of DFB on vegetation and various organisms after the aerial application of 28 g/acre to oak-pine and oak-hickory forests. Initial residues on vegetation (1 day after treatment) were 0.45 mg/kg. These decreased to 0.18 mg/kg by day 21. The half-time for the decay (calculated from tabulated data in the study), is about 17 days, which is similar to reported values for surface residues (Nigg and others 1986). The pattern of decay is relatively complex and is not well described by a first order model (Martinat and others 1987). An initial decrease in residues was associated with precipitation; however, subsequent rainfall did not cause the levels of DFB to decrease further. A similar pattern was observed in a hardwood forest after aerial spraying with 0.03 pounds ai/acre (13.6 g ai/acre) DFB (Dimilin 25W) (Wimmer and others 1993). Initial levels on trees ranged from 2.9 to 75 ng/cm^2, depending on the tree species and canopy location.

Generally, higher levels were found in the upper canopy. During the first 3 weeks after application, residues decreased by 20%–80%, after which time there was little decrease in the amount of residues. As discussed in section 6.3.2.5 on contaminated water, this kind of biphasic decay is reported in much of the monitoring data on water. In a companion publication, Harrahy and others (1993) demonstrated that the persistent residue on leaves can serve as a sink for eventual environmental contamination by DFB at leaf fall.

USDA (1980) reports that residues ranged from 0 to 11.25 mg/kg in vegetation after Dimilin was applied at a rate of 6.8 g/acre. Lesser amounts, 0–4.73 mg/kg, were detected in crops.

Two types of exposure scenarios are considered, one for toxic effects and the other for carcinogenic effects. For toxic effects, the maximum monitored residue on vegetation is used. The maximum residue is from a monitoring study (USDA 1980) in which residues ranging from 0 to 11.25 mg/kg were detected in vegetation after Dimilin was applied at a rate of 6.8 g/acre. Assuming that residues are proportional to application rates, the maximum residue at an application rate of 28 g/acre is estimated to be approximately 50 mg/kg

$$(28 \text{ g/acre} \div 6.8 \text{ g/acre}) \cdot 11.25 \text{ mg/kg} = 46 \text{ mg/kg}.$$

For the extreme exposure scenario for toxic effects, it will be assumed that all of the consumed vegetation is contaminated. The mean consumption of vegetation for a 70 kg man is 0.051 kg/day, and the 95% upper limit on consumption is 0.173 kg/day (U.S. EPA 1989d). Thus, the average dose of DFB is estimated as 0.036 mg/kg

$$50 \text{ mg/kg} \cdot 0.051 \text{ kg/day} \div 70 \text{ kg} = 0.036 \text{ mg/kg}.$$

The maximum dose is estimated as 0.124 mg/kg

$$50 \text{ mg/kg} \cdot 0.173 \text{ kg/day} \div 70 \text{ kg} = 0.124 \text{ mg/kg}.$$

For the routine exposure scenario, it will be assumed that only home grown vegetation is contaminated. The mean consumption of home grown vegetation for a 70 kg man is 0.0045 kg/day, and the 95% upper limit on consumption is 0.0144 (U.S. EPA 1989d). Thus, the estimated average dose is 0.0032 mg/kg

$$50 \text{ mg/kg} \cdot 0.0045 \text{ kg/day} \div 70 \text{ kg} = 0.0032 \text{ mg/kg}.$$

The estimated maximum dose is 0.010 mg/kg

$$50 \text{ mg/kg} \cdot 0.0144 \text{ kg/day} \div 70 \text{ kg} = 0.010 \text{ mg/kg}.$$

For prolonged exposures in which carcinogenic effects are considered, it is not plausible to use the upper limit of residues on vegetation; hence, for this assessment, 30 mg/kg will be

used. This is within the range of concentrations observed in two studies (Austin and Carer 1986, Carr and others 1990). Other studies, however, have reported much lower concentrations (Martinat and others 1987, Schroeder and others 1980). Thus, the use of 30 mg/kg as an initial residue on vegetation is conservative, but somewhat less so than taking the maximum residue.

For carcinogenic effects, the average daily dose over the course of 1 year will be calculated using half-times on plants ranging from 20 to 30 days, values which bracket the range of reported observations. First order kinetics will be assumed. This again is conservative because most detailed monitoring studies suggest an initial rapid decrease on vegetation. Using these assumptions, residues at the end of 1 year are estimated to range from 0.00053 to 0.020 mg/kg. Thus, the average daily dose is the geometric mean of the initial value, 30 mg/kg, and these terminal values. The lower mean value, which will be used for the routine scenario, is 0.12 mg/kg. The upper mean value, which will be used for the extreme scenario, is 0.77 mg/kg. For both scenarios, it will be assumed that only home grown vegetables are consumed. For the routine scenario, the daily dose is $7.7 \cdot 10^{-6}$ mg/kg

$$0.12 \text{ mg/kg} \cdot 0.0045 \text{ kg/day} \div 70 \text{ kg} = 7.7 \cdot 10^{-6} \text{ mg/kg},$$

using the mean daily consumption of home grown vegetables. For the extreme scenario, the daily dose is $1.6 \cdot 10^{-4}$ mg/kg

$$0.77 \text{ mg/kg} \cdot 0.0144 \text{ kg/day} \div 70 \text{ kg} = 1.6 \cdot 10^{-4} \text{ mg/kg},$$

using the 95% upper limit on the daily consumption of home grown vegetables.

6.3.2.8. Consumption of Contaminated Animals and Animal Products

These scenarios assume that the general public may be exposed to DFB by consuming the flesh or milk of contaminated cattle or by consuming contaminated game. No detectable levels of DFB were found in meat from cattle given an oral dose of DFB (Ivie and others 1978). Based on these data, one would not expect DFB in the flesh of cattle or game mammals exposed to ground or aerial applications of DFB. Nevertheless, after cows were given an oral dose of 10 mg/kg DFB, the levels in their milk were as high as 0.8 mg/L (Ivie and others 1978).

Assuming that the amount that a cow eats per day is equal to approximately 5% of its body weight (U.S. EPA 1987c) and that DFB residues may be as high as 50 mg/kg on the vegetation eaten by cows, the daily dose of DFB for a cow immediately after spraying would be 2.5 mg/kg/day (50 mg/kg · 0.05). This is reasonably close to the oral dose used in the study by Ivie and others (1978); therefore, it seems reasonable to estimate the concentration in milk at 0.2 mg/L

$$0.8 \text{ mg/L} \cdot 2.5 \text{ mg/kg/day} \div 10 \text{ mg/kg/day} = 0.2 \text{ mg/L}.$$

For a 10 kg child consuming 1 L of milk per day (U.S. EPA 1989d), the dose would be 0.02 mg/kg

$$0.2 \text{ mg/L} \cdot 1 \text{ L} \div 10 \text{ kg} = 0.02 \text{ mg/kg}.$$

This scenario may be considered extreme because it would occur only immediately after spraying and uses upper limits on monitored residues in vegetation.

A more typical exposure scenario involving the consumption of contaminated milk can be based on the annual average level in vegetation (0.77 mg/kg) derived above. This is still somewhat conservative, because this value is derived from the upper range of the half-times on vegetation. Using this value, the average daily dose for the cow would be 0.04 mg/kg (0.77 mg/kg · 0.05) and the level in milk would be 0.0032 mg/L

$$0.8 \text{ mg/L} \cdot 0.04 \text{ mg/kg/day} \div 10 \text{ mg/kg/day} = 0.0032 \text{ mg/L}.$$

This exposure estimate is intended to estimate lifetime cancer risks, so a 70 kg body weight will be used for an adult male. Thus, the average daily dose would be $4.6 \cdot 10^{-5}$ mg/kg

$$0.0032 \text{ mg/L} \cdot 1 \text{ L} \div 70 \text{ kg} = 4.6 \cdot 10^{-5} \text{ mg/kg}.$$

There were detectable levels of DFB in the breast tissue of chickens given oral doses of the compound (Opdyke and others 1982b). In addition, there were detectable levels of DFB in 2 of 38 birds (based on whole body residues) after Dimilin applications (USDA 1980). The highest level, 0.036 mg/kg, was found in a kingbird. The whole body residue may not reflect levels in the muscle tissue since it is likely that at least some DFB was on the feathers and in the viscera. Hence, 0.036 mg/kg is a conservative estimate of residue levels in tissue. Using this residue as an upper limit for levels in the edible flesh of game birds and assuming that a 70 kg male would consume 1 pound (0.453 kg), the dose would be 0.0002 mg/kg

$$0.036 \text{ mg/kg} \cdot 0.452 \text{ kg} \div 70 \text{ kg} = 0.0002 \text{ mg/kg}.$$

6.4. Dose-Response Assessment

Based on the hazard identification, dose-response relationships will be derived for two endpoints, hematological effects and carcinogenicity. For both effects, separate assessments will be made of the dose-response relationships for DFB and 4-chloroaniline.

6.4.1. Hematological Effects

6.4.1.1. Diflubenzuron

The reference dose (RfD) for DFB is 0.02 mg/kg/day (U.S. EPA 1994a). The critical effect for this RfD is the formation of methemoglobin and sulfhemoglobin. This RfD is based on a 1-year dog feeding study in which the no-observed-effect level (NOEL) was 2 mg/kg/day and the lowest-observed-adverse-effect level (LOAEL) was 10 mg/kg/day (Duphar 1985). The NOEL is divided by an uncertainty factor of 100 to derive the RfD. The uncertainty factor of 100 is intended to account for intra- and interspecies differences. Confidence in the principal study, the database for toxic effects, and the RfD itself is high (U.S. EPA 1994a). The RfD was reviewed by U.S. EPA in September, 1990. Since that time, there have been no data located in the literature to alter this assessment. Discussions with George Ghali, the U.S. EPA contact for this compound [U.S. EPA, Office of Pesticide Programs, (703)305-7490], indicate that no review of this compound by the RfD Work Group is anticipated.

For this risk assessment, the RfD will be accepted as the RRV for the general public as well as workers and used without modification. Because the RfD is intended to protect for lifetime exposures, it provides a conservative basis for comparing estimated exposure levels to an index of acceptable exposure. In other words, if projected levels of exposure are below this level for an exposure scenario, no adverse effects are anticipated, even if the exposure continued over a lifetime.

In assessing risks above the RRV, the most important issue is the relationship of the formation of methemoglobin and sulfhemoglobin to clinically significant adverse effects. The best dose-response data available are on mice. In a long-term feeding study using mice, levels of methemoglobin were approximately 1% in mice that were not exposed to DFB (Keet 1984b). At doses of almost 1,000 mg/kg, the levels of methemoglobin increased to approximately 6%. The overall relationship is illustrated in Figure 6-5. The available dose response relationships for other species are summarized in Table 6-5. No gross signs of toxicity were apparent in any of the animals.

Normal levels of methemoglobin in humans and the clinical consequences of increased levels of methemoglobin are reasonably well characterized (Table 6-6). The clinical significance of varying levels of sulfhemoglobin is less well characterized. In normal human populations, levels of methemoglobin range from about 0.6% to somewhat less than 4%. Some but not all studies indicate that levels tend to be higher in smokers, compared with nonsmokers. At levels of approximately 10%, blood is dark brown in appearance, indicating an impaired ability to transport oxygen; however, clinical signs of frank toxicity at this level have not been reported (Jaffe 1981). At levels between 20% and 45%, signs of toxicity, such as cyanosis, are apparent and require medical intervention. Levels as low as 50% have been

characterized as **life threatening** (Daly and others 1983). Levels greater than 70% clearly are life threatening (Jaffe 1981).

6.4.1.2. 4-Chloroaniline

The RfD for 4-chloroaniline is 0.004 mg/kg/day (U.S. EPA 1994a). The critical effect for this RfD is the formation of non-neoplastic lesions of the splenic capsule in rats. This RfD is based on a 2-year feeding study in rats in which the critical effect was observed at the lowest dose tested, 250 ppm in the diet (12.5 mg/kg/day) (NCI 1979). The LOAEL is divided by an uncertainty factor of 3,000 to derive the RfD. This uncertainty factor is intended to account for intra- and interspecies differences and the extrapolation from a LOAEL to a NOAEL. An additional factor of 3 was incorporated into the uncertainty factor because of the lack of supporting reproductive and other toxicity data. Confidence in the principal study, the database for toxic effects, and the RfD itself is low (U.S. EPA 1994a).

For this risk assessment, the RfD will be accepted as the RRV for the general public and used without modification. As with the RfD for DFB, this provides a conservative basis for comparing estimated exposure levels to an index of acceptable exposure.

6.4.2. Carcinogenicity

6.4.2.1. Carcinogenic Potency of 4-Chloroaniline

Calculating the potential carcinogenicity of 4-chloroaniline is relatively simple. The database has not changed since the previous environmental impact statement for the gypsy moth program (U.S. Department of Agriculture, Forest Service 1985 and 1989). Hence, the dose-response assessment for the carcinogenicity of 4-chloroaniline will be based on the NCI bioassay. In the 1985 environmental impact statement, however, the dose-response assessment uses point estimates, ignoring doses that yielded 0% response, based on the simple linear model:

$$p = \alpha + \beta \cdot d$$

where:
p = *cancer risk*
α = *background response*
β = *cancer potency*
d = *dose*

(18)

In addition, the previous assessment used the cancer data from male mice and rats and used matched control data instead of historical control data. Furthermore, after adjusting for

species extrapolation by the cube root of the body weight ratios, it took the arithmetic mean of the two estimates of potency, 0.019 $(mg/kg/day)^{-1}$, as the cancer potency for the risk assessment.

This assessment uses the linearized multistage model and general procedures outlined by U.S. EPA (1986a), as discussed in section 2. Other differences between this assessment the previous one is that this assessment uses only the dose-response data for male rats and only data from historical controls. The data on mice are not used because the male rats were the only test group that had a clear carcinogenic response. Even if the mice data were considered, the potency estimates would be much lower than the potency estimates for rats. Thus, the conservative and prudent approach is to use the most sensitive species unless additional considerations suggest that an alternative species is more appropriate (U.S. EPA 1986a). There are no data to suggest that mice are more appropriate than rats for dose-response assessments involving exposure to 4-chloroaniline. Data from historical controls are used because the observed tumors are rare and because the historical data are the basis for the hazard identification. In this case, the use of historical controls is also more conservative.

Dietary exposure levels of 0, 250, and 500 ppm and their corresponding response rates, 1/360, 0/49, and 10/49 were used in the multistage model. The resulting estimate of potency (q_1^*) based on the 95% upper limit of response is 0.00011 ppm^{-1}. The maximum likelihood estimates from the model are: $q_0 = 2.45 \cdot 10^{-3}$ and $q_6 = 1.42 \cdot 10^{-17}$. Assuming that rats, over the course of a lifetime study, consume an average of 5% of their body weight in food each day (U.S. EPA 1989c), the q_1^* can be converted to 0.0022 $(mg/kg/day)^{-1}$

$$0.00011\ ppm^{-1} \div (0.05\ mg/kg/day \div ppm) = 0.0022\ (mg/kg/day)^{-1}.$$

The average weight of the male rats over the course of the study is estimated at 350 g from the growth curve provided in the study (NCI 1979). The q_1^* for the rat is used to estimate a cancer potency for humans of 0.013 $(mg/kg/day)^{-1}$

$$0.0022\ (mg/kg/day)^{-1} \cdot (70\ kg \div 0.35\ kg)^{0.33} = 0.013\ (mg/kg/day)^{-1},$$

using 70 kg as an average human body weight. This estimate is very close to the 0.019 $(mg/kg/day)^{-1}$ derived in the 1985 environmental impact statement.

6.4.2.2. Carcinogenic Potency of Diflubenzuron

Quantification of the potential carcinogenicity of DFB involving direct exposure is a much more difficult problem than the assessment of 4-chloroaniline. Methods for estimating carcinogenic risk for a compound that is metabolized to a carcinogen but negative in cancer bioassays have not been proposed. U.S. EPA has used a toxic equivalency factor approach for some chemical classes (for example, U.S. EPA 1989e). This method is used to estimate

carcinogenic potencies for a class of compounds based on the carcinogenic potency of one or more members of the class. Other information (for example, reproductive toxicity, binding affinity) is used judgmentally to estimate the carcinogenic potency of other class members. With modification, these methods can be used to estimate the carcinogenic potency of DFB on the basis of the carcinogenic potency of 4-chloroaniline. Two kinds of data are useful, the relative amounts of DFB converted to 4-chloroaniline and the relative hematological potency of these compounds. Furthermore, the carcinogenicity of DFB can be assessed based on the negative bioassay using an upper estimate of response. The data on the mutagenicity of 4-chloroaniline and DFB are not comparable; therefore, a relative-potency method based on mutagenic activity cannot be used.

Metabolism

Studies regarding metabolism of DFB indicate that approximately 1% or less of the administered dose is recovered as 4-chloroaniline (Opdycke and others 1982a and 1982b). For this analysis, 1% will be used as an upper range of the amount of DFB that might be metabolized to 4-chloroaniline. The 4-chloroaniline dose that elicited a carcinogenic response in the rats was 500 ppm (that is, 500 mg of DFB per kg of diet) over a 2-year period (NCI 1979). An equivalent dose for DFB might be calculated as 50,000 ppm (500 ÷ 0.01), assuming that DFB has only 1% of the carcinogenic potency of 4-chloroaniline because only 1% of DFB is converted to 4-chloroaniline. Each of the dietary concentrations used in the rat study on DFB (156, 625, 2,500, and 10,000 ppm) is below this level (Keet 1984a). Thus, it might be argued that the doses used in the rat bioassay were not sufficiently high to detect the carcinogenic potential of DFB. Using this approach, the cancer potency for DFB would be estimated at 0.00013 $(mg/kg/day)^{-1}$ [0.013 $(mg/kg/day)^{-1}$ · 0.01], the carcinogenic potency 4-chloroaniline times the estimated relative potency of DFB with respect to 4-chloroaniline.

This estimate of cancer potency based on metabolism studies is extremely simplistic and implies a series of linear relationships that probably are not true. First, it has been demonstrated that the oral absorption of DFB is inversely related to dose (Williams and others 1980). Thus, at lower doses, a greater proportion of DFB in the diet will be absorbed. How much of this is converted to 4-chloroaniline cannot be determined from the available data. Second, in order to estimate a dietary concentration of DFB equivalent to a dietary concentration of 4-chloroaniline that induces splenic tumors requires pharmacokinetics and distribution data which are not available.

Relative Hematological Potency

The only available studies regarding the induction of methemoglobinemia or sulfhemoglobinemia by 4-chloroaniline involve acute exposure. A single oral dose of 0.0625 mmol/kg of 4-chloroaniline induced methemoglobinemia (an increase of approximately 60%

above controls) in five cats (sex not specified). In the only available study involving acute exposure to DFB, marginal methemoglobinemia and sulfhemoglobinemia were observed in rats exposed to 5,000 mg/kg/day (16.1 mmoles/kg/day) of the compound by gavage for 8 days (Keet 1977a). Taking these two data points as approximately equitoxic doses, the potency of DFB relative to 4-chloroaniline is 0.004 (0.0625 ÷ 16.1) on a molar basis or 0.0016 (8 ÷ 5,000) on a weight basis (molecular weight of 4-chloroaniline = 127.57). Since the cancer potency is expressed in weight rather than moles, the latter value is used to estimate a potency of 0.000021 $(mg/kg/day)^{-1}$ [0.0016 · 0.013 $(mg/kg/day)^{-1}$].

Use of the Negative Bioassay

In the cancer bioassays on DFB, the highest dose tested was in male rats, 453 mg/kg/day (Keet 1984a). At this dose, pigment macrophage changes were seen in the spleen; however, none of the 29 surviving male rats had any form of cancer. The upper 95% limit on a response rate of 0/29 is approximately 0.12. Using this value in the simple linear model, the carcinogenic potency is 0.00026 $(mg/kg/day)^{-1}$ (0.12 ÷ 453 mg/kg/day). The cubed route of the body weight ratios can be used to estimate a human potency of 0.0015 $(mg/kg/day)^{-1}$

$$0.00026\ (mg/kg/day)^{-1} \cdot (70 \div 0.35)^{1\div3}.$$

Hence, the relative potency of DFB with respect to 4-chloroaniline is 0.1 (0.0015 ÷ 0.013).

This relative potency estimate, however, is not consistent with the available data. Assuming a potency of 0.1, the highest dose in the bioassay on DFB (10,000 ppm) would be considered equivalent to 1,000 ppm (10,000 ppm · 0.1) of 4-chloroaniline. Using the results from the multistage model for the bioassay on male rats exposed to 4-chloroaniline, the expected response at a dietary level of 1,000 ppm is greater than 99% and the expected response for the DFB assay at 1,000 ppm is 29/29. As noted, the observed response was 0/29. This is not quite as incongruous as it seems because the potency estimate is based on an upper limit of response; therefore, it is inherently conservative; in other words, it is likely to overestimate risk. Nonetheless, this highly conservative estimate of relative potency is incongruous with the estimates based on the other methods.

As an alternative, assume that the number of animals used in the high dose group of the cancer bioassay on DFB was marginally insufficient to detect a response and that if one additional animal had been used, it would have developed a tumor, making the response in the high dose group 1/30. Using 1/30 in the simple linear model, the carcinogenic potency is 0.000073 $(mg/kg/day)^{-1}$ (0.033 ÷ 453 mg/kg/day). The cubed route of the body weight ratios can be used to estimate a human potency of 0.00043 $(mg/kg/day)^{-1}$

$$0.000074\ (mg/kg/day)^{-1} \cdot (70 \div 0.35)^{1\div3}.$$

Based on this estimate, the relative potency of DFB with respect to 4-chloroaniline is 0.03 (0.00043 ÷ 0.013). As with the other estimates, this potency is consistent with the available data on DFB and 4-chloroaniline. Assuming a relative potency of 0.03, the highest dose of DFB (10,000 ppm) would be equivalent to 300 ppm (10,000 ppm · 0.03) 4-chloroaniline. Using the results from the multistage model for the bioassay on male rats exposed to 4-chloroaniline, the expected response at a dietary level of 300 ppm is 0%, which is consistent with the results of the DFB bioassay.

Selection of DFB Cancer Potency for Dose-Response Assessment

Comparing the analyses described above and excluding the inconsistent analysis based on upper limits of risk from the negative DFB bioassay yields a range of estimates within an order of magnitude of one another:

Method	Relative Potency (4-CA ÷ DFB)	Cancer Potency ($mg/kg/day^{-1}$)
Metabolism	0.01	0.00013
Hematopoietic Effects	0.004	0.000021
Negative Bioassay	0.03	0.00043

None of these estimates can be identified as better or worse than any other. For the current risk assessment, the risk characterization uses the range of the cancer potency estimates for DFB characterized above. It uses the geometric mean of the estimates, 0.0001 $(mg/kg/day)^{-1}$, as the central value and the observed range to bracket the uncertainty.

6.5. Risk Characterization

6.5.1. Overview

As discussed in the hazard identification (see section 6.2), exposure to DFB is clearly associated with methemoglobinemia. This appears to be the most sensitive effect (that is, the effect that occurs at the lowest dose level). DFB can induce methemoglobinemia, which impairs the ability of the blood to function normally and can be life threatening at high levels. As discussed in the dose-response assessment (see section 6.4), RRVs for this effect can be derived for both workers and the general public. RRVs represent the highest dose levels that will not induce this effect. Based on estimates of daily dose derived in the exposure assessment, the risk associated with methemoglobinemia is characterized as an HQ (that is, the estimated level of exposure divided by the RRV). When this ratio is below unity (in other words, the level of exposure is less than the RRV), the effect is not anticipated and concern is minimal. As this ratio exceeds unity, however, concern increases. The

relationship of dose levels greater than the RRV to the development of clinically significant effects is discussed in the dose-response assessment (see section 6.4) and summarized in Table 6-6.

The available data do not indicate that DFB is a carcinogen. Nonetheless, 4-chloroaniline, a chemical substance into which DFB is changed in the body, in soil, and in water (in other words, a mammalian or environmental metabolite of DFB) may be a carcinogen. For this risk assessment, estimates of carcinogenic potency are made for both DFB and 4-chloroaniline in the dose-response assessment (see section 6.4). Cancer risk is expressed as the probability of observing cancer in a population exposed to a specified dose over an entire life span. As detailed in the dose-response assessment (see section 6.3), a consideration of the potential carcinogenic activity of DFB is made under the assumption that DFB may be converted to 4-chloroaniline in the body and that this conversion could pose a potential carcinogenic risk. This is an extremely conservative approach designed to illustrate the highest conceivable potential risk. The most likely estimate of the carcinogenic risk of direct exposure to DFB is zero. In other words, as detailed in the hazard identification, DFB has not been classified as a carcinogen.

Numerical expressions of risk, which are the basis of any risk characterization, often suggest a level of precision or accuracy that is seldom justified by the available data. Consequently, this section begins with a discussion of the major sources of uncertainty and the impact that these uncertainties have on the interpretation of the likely human health consequences of exposure to DFB in gypsy moth control programs. This discussion is followed by a summary of the potential effects in workers, the general public, and groups that may be at increased risk.

6.5.2. Sources of Uncertainty

The dermal absorption of DFB, the dose-severity relationships for effects of DFB on the blood, and the potential cancer risk associated with DFB are the predominant sources of uncertainty in the assessment of the human health consequences of exposures to DFB.

6.5.2.1. Dermal Absorption

All exposure assessments for workers and several exposure assessments for the general public require estimates of dermal absorption. Two types of dermal absorption estimates are used, depending on the nature of the exposure. Some exposures can be characterized as contact with DFB in a liquid at a virtually constant concentration for a specified period of time. Examples of such exposures include immersion of all or part of the body in a liquid formulation of DFB or wearing clothing saturated with a liquid formulation of the compound. In other cases, exposures can be characterized as a relatively small amount of DFB (not necessarily in liquid form) placed on or transferred to the skin. Examples of these exposures

include skin contact with contaminated vegetation, accidental spills on the skin, and spray making direct contact with the skin.

There are widely used and accepted methods for estimating the amount of chemical absorbed by the skin after either type of dermal exposure. For exposures to liquid formulations at constant concentrations, as discussed in section 6.3 on exposure assessment, K_p are used to estimate the rate of absorption. Although experimental measurements of K_p are not available for DFB, reliable methods have been developed for estimating K_p values based on the physical properties of various chemicals. These methods, however, apply only to solutions of the chemical. For dermal exposures to relatively small amounts of DFB, there are methods for estimating the proportion of the applied chemical that will be absorbed during a particular period of time (Rubin and others 1994).

Exposure to DFB usually involves dermal contact with a commercial formulation such as Dimilin 4L or Dimilin 25W. Dimilin 4L is a liquid formulation containing 479 g of DFB/L. The water solubility of DFB is approximately 0.1 mg/L. DFB is only partially dissolved in this commercial formulation, with most of the compound present as particulate matter that will not be readily absorbed.

6.5.2.2. Effects on the Blood

There is no doubt that DFB causes effects on the blood including the formation of methemoglobinemia and sulfhemoglobinemia. These effects probably occur through the metabolic formation of 4-chloroaniline, a metabolite of DFB that has been shown to cause these effects in laboratory animals. As discussed in section 6.2 on hazard identification, these effects impair the ability of the blood to carry oxygen. Secondary effects include the formation of Heinz bodies and enlargement of the spleen. The ability of DFB to induce these effects has been demonstrated in studies with mice, rats, rabbits, cats, dogs, and sheep (Keet and others 1982).

There are no reports of human poisoning by DFB in the available literature. Nonetheless, there are data on several compounds demonstrating that chemicals that induce methemoglobinemia and sulfhemoglobinemia in experimental mammals will induce similar effects in humans (Jaffe 1981). Thus, it is reasonable to assume that exposure to DFB will be associated with increased levels of methemoglobin and sulfhemoglobin in humans.

As discussed in the dose-response assessment (see section 6.4), the available studies involving oral exposure to DFB do not include methemoglobinemia levels that are considered clinically significant. Dose levels ranging up to approximately 1,000 mg/kg have been associated with methemoglobin levels of about 10% or less. Extrapolation from these doses to doses that may cause clinically significant levels of methemoglobin in animals or humans is uncertain, particularly in view of the low absorption rate of DFB after oral administration of high doses. To address these uncertainties requires clinical studies in which humans are

exposed to low dose levels of DFB and additional studies in which animals are exposed to dose levels greater than 1,000 mg/kg/day.

6.5.2.3. Carcinogenicity

As discussed in the hazard identification (see section 6.2), DFB has been tested for carcinogenicity and there is no indication that DFB causes cancer in any species. Although a metabolite of DFB, 4-chloroaniline, yielded a carcinogenic response in a whole animal bioassay, the weight of evidence for the carcinogenicity of this compound is limited. The results of in vitro assays for mutagenicity are inconclusive for DFB and 4-chloroaniline.

In the section 6.4 on dose-response assessment, the upper limit for the carcinogenic potency of 4-chloroaniline has been estimated on the basis of the positive results observed in the whole animal bioassay. The potency estimate for humans is 0.013 $(mg/kg/day)^{-1}$. This estimate assumes a lifetime exposure for a 70 kg man (approximately 154 pounds). The method used to extrapolate the animal data to humans requires the use of an estimate for human body weight. In this case, the body weight of the male is used. This is more conservative, although only slightly so, than potency estimates based on the average female body weight. This is an area of minor uncertainty. Far more uncertain is the use of life span potency estimates to calculate risk from less than life span exposures, which involves taking doses administered over a relatively short time period and adjusting them by the ratio of the duration of exposure to the life span. As this ratio decreases, uncertainty in the assessment increases. The magnitude of the uncertainty, however, cannot be characterized.

Section 6.4, the dose-response assessment, also estimates a cancer potency for DFB. As indicated above, the available whole animal bioassays on DFB do not indicate that this compound is carcinogenic. Nonetheless, because DFB is metabolized to 4-chloroaniline and because the carcinogenicity of 4-chloroaniline is considered in this risk assessment, the potential carcinogenicity of DFB is addressed. Based on an analysis of the negative bioassay on DFB and the positive bioassay on 4-chloroaniline, and assuming that any cancer-causing activity of DFB is due to the formation of 4-chloroaniline, a case can be made for concluding that the negative result in the DFB bioassay is attributable to the use of low doses relative to the likely carcinogenic potency of DFB. Based on the relative biological activities of DFB and 4-chloroaniline and the conversion of DFB to 4-chloroaniline in vivo, the cancer potency of DFB for the assessment of human health risks is estimated at 0.0001 $(mg/kg/day)^{-1}$, about 1% of the potency of 4-chloroaniline. The range on this estimate is 0.00002–0.0004 $(mg/kg/day)^{-1}$. This variability of a factor of 20 accounts for differences in the available types of data that can be used but does not address the uncertainty inherent in treating DFB as a carcinogen.

The cancer risk estimates for 4-chloroaniline and DFB given in this section are intended to illustrate the results of a very conservative set of assumptions used to evaluate the available data. It is highly unlikely that exposure to DFB as a result of gypsy moth control procedures

causes cancer. Addressing this uncertainty will require additional bioassays on the carcinogenicity of DFB using dose levels that are higher than those investigated. In addition, it would be useful to have bioassays of 4-chloroaniline in species other than those already tested. The question of whether such bioassays are worth conducting, given the cost of these tests and the need to test other compounds of potentially greater concern, is beyond the scope of this assessment.

6.5.3. Workers

The risk characterizations for workers are summarized in Table 6-7. As noted in the dose-response assessment (see section 6.4), the RRV for Dimilin is 0.02 mg/kg/day. The cancer risk, based on the upper limit for the carcinogenic potency of DFB, is $4 \cdot 10^{-4}$. Risks based on the central estimate of carcinogenic potency ($1 \cdot 10^{-4}$) would be a factor of 4 less than the risks given in Table 6-7. The dose given in the second column cannot be used directly to estimate cancer risk because the potency estimates are based on average daily doses over a life span. In order to estimate the average daily life span doses equivalent to those derived for each scenario, the scenario specific dose is multiplied by the ratio of the number of days that the exposures may occur in a life span divided by the reference human life span in days.

Individual spray programs generally last for a couple of weeks; nonetheless, individuals may work on several programs in the course of one season. Thus, worker exposure scenarios are based on the assumption that a worker is involved in various programs for 2 months/year, working 7 days/week, for a period of 20 years. This assumption is intentionally conservative. Although some individuals might work on gypsy moth spray programs for more than 20 years, very few will work for 2 months each year and even fewer will work 7 days/week for the entire spray season. Thus, the adjustment on risk for most worker scenarios is 0.05

$$(2 \text{ months/year} \div 12 \text{ months/year}) \cdot (20 \text{ years} \div 70 \text{ years}) = 0.05.$$

For the accident scenarios, increased lifetime risks per event are given. Thus, the adjustment on risk is 0.0008

$$(1 \text{ event/day} \div 365 \text{ days/year}) \cdot (20 \text{ years} \div 70 \text{ years}) = 0.0008.$$

The adjustment factor is applied only to cancer risk. The HQs, which apply to toxic effects other than cancer, represent risks associated with constant exposure over a lifetime to the doses specified in the second column of Table 6-7.

Cancer risks are not derived for extreme exposure scenarios. These upper range exposures are intended to represent transient maximum exposures, based on an understanding of the variabilities inherent in each scenario. Although extreme scenarios are appropriate for

assessing potential toxic effects, it is not plausible to assume that worst case exposure assumptions will persist for prolonged periods of time.

The highest cancer risk for workers (based on conservative upper limits of potency) is 3 in 10 million. Given the uncertainties regarding a qualitative assessment of the carcinogenicity of DFB and these low risk estimates, cancer is not considered a significant endpoint in assessing the consequences of worker exposure to DFB.

Routine exposure scenarios do not involve exposures that exceed an HQ of unity, which would suggest a potential for concern. Two extreme exposure scenarios for workers result in HQs of 3. As detailed below, this HQ might be associated with a detectable increase in methemoglobin but is not likely to be associated with any significant clinical effect.

One of the four accidental exposure scenarios leads to HQs greater than unity. Immersion exposures are less hazardous than accidental spills because little DFB will be in solution. The typical spill scenario assumes that the material is spilled on the lower legs, and that the legs are washed thoroughly after 1 hour. The resulting HQ is below the level of concern. The extreme scenario is based on an identical spill, but assumes that the legs are not washed thoroughly and that absorption continues for 24 hours. The resulting HQ is 40.

Although an HQ of 40 is relatively high, the dose-response relationships for methemoglobinemia in experimental mammals are not steep. Based on these relationships, HQs in the range of 40, which are associated with a dose of 0.8 mg/kg, might be associated with an increase in the methemoglobin level to about 2%–4%. As illustrated in Figure 6-5, this estimate assumes that humans are 10 to 100 times more sensitive than mice. As discussed in the dose-response assessment (see section 6.4), methemoglobin levels of 2%-4% are less than those associated with any clinically detectable effect and well below the levels associated with toxic effects. There are, however, no data regarding the dose-response relationships of DFB-induced methemoglobinemia in humans, and this adds substantial uncertainty to the assessment of the potential effects of this exposure scenario.

6.5.4. General Public

The risk characterizations for the general public are summarized in Table 6-8, which is identical in format to Table 6-7. Most of the data presented in Table 6-8 are single source exposure scenarios; however, two multiple source exposure scenarios are provided, one for the period immediately after spraying and the other for prolonged exposure, intended to reflect residual time-weighted average doses over the course of an entire year.

General public exposure scenarios are based on the assumption that the individual lives in an area that is part of a control program every year and that one application at the maximum rate of 28 g/acre is made in each program. For the direct exposures, one event per application is assumed. Thus, the adjustment factor on cancer risk is 0.003

(1 application/year ÷ 365 days/year). This is identical to the approach taken for accidental exposures in workers.

For the consumption of ambient water and the consumption of contaminated fish, risk is time weighted to reflect changes in exposure over time. For water, an initial level of 10 μg/L is used. This level is assumed to decrease to 0.1 μg/L after 2 weeks and remain as such for as many as 10 months after application. The level in water after that time is assumed to be 0 until the next application. This approach is used because some studies have shown that water levels of DFB are relatively stable, after an initial dispersion and dilution, for as long as 10 months after Dimilin spray. For fish, a similar approach is used, based on available monitoring data. Three time periods are considered in estimating time-weighted average levels. First is the 2-week period during which levels in fish are the highest. Then, there is a 2-week period during which levels in fish decrease by a factor of 10. Finally, there is a period that lasts until 10 months after spraying during which levels in fish parallel those in water and a 2-month period during which no residues in fish are anticipated. For water consumption, the level of 4-chloroaniline in water is taken at 10% of the expected level of DFB. For fish consumption, the level of 4-chloroaniline in fish is taken at 1% of the expected level of DFB. Both of these values are based on monitoring data. As indicated in Table 6-8, none of the exposure scenarios for ambient water or fish caught from ambient water approach a level of concern.

None of the cancer risks for single source scenarios exceed 7 in 10 million. The only single source scenarios with HQs at unity or greater involve ejection of the entire spray load from the aircraft, consumption of contaminated vegetation, and the consumption of milk from cows eating contaminated vegetation.

The scenarios involving the ejection of an entire load by the aircraft during an emergency are accompanied by all of the uncertainties associated with dermal absorption. Another source of variability is the dilution of Dimilin in the aircraft. For this assessment, it is assumed that a spray volume of 0.5 gallons/acre is used and that each gallon contains 28 g of DFB. This is the lowest dilution rate used in aerial sprays; therefore, it poses the greatest risk. As the spray volume is increased, the dilution rate increases, and the associated decrease in risk is linear. Thus, at a spray volume of 1 gallon/acre, the risks for both toxic and carcinogenic effects will be one half of those presented in Table 6-8. Each of these scenarios is based on the assumption that a child is drenched by the ejected load and that the chemical is removed from the skin after 1 hour.

The HQ of 0.2 associated with uptake from contaminated surfaces immediately after spraying is affected also by the uncertainties associated with dermal absorption. In other respects, there is relatively little uncertainty associated with these estimates. Monitoring data are available on transfer rates from contaminated surfaces to skin and clothing, and these estimates are in relatively good agreement with empirical estimates of the relationship of transfer rates to dislodgeable residues. These analyses indicate that uptake from contaminated surfaces is not of concern even immediately after spraying.

The consumption of game animals or farm animals exposed to DFB is of relatively little concern. The available data, albeit limited, suggest that mammals will not concentrate detectable levels of DFB in muscle tissue. Therefore, consuming deer or cattle exposed to DFB does not present a substantial risk. On the other hand, fowl exposed to DFB may have detectable levels of the compound in their muscle tissue.

The major concern regarding human exposure to DFB from contaminated animals involves the occurrence of DFB in cows' milk. Milk may become contaminated when cows graze on vegetation sprayed with DFB. Immediately after spraying, DFB levels on vegetation may be high enough to produce DFB levels in milk that represent a marginal risk for the child who consumes 1 L milk/day. The cancer risk in the routine exposure scenario involving the consumption of cows' milk is greater than the cancer risk in the exposure scenario involving the consumption of cows' milk that contains the maximum level of DFB (Table 6-8). This is because the lifetime risk from the maximum level is reduced by a time-weighting of the dose, as discussed above, whereas the risk associated with the routine exposure scenario is based on an estimated lifetime average daily dose and is not adjusted. Nonetheless, this lifetime risk is low (approximately 2 in 100 million). For most cases, even this low risk level is probably an overestimate because most individuals would not consume contaminated milk from a single farm over an entire season. In addition, this is regarded as an accidental rather than routine exposure because Dimilin is not intentionally applied to pasture land.

The greatest number of exposures and correspondingly high HQs occur from the consumption of contaminated vegetation. There is relatively little uncertainty associated with the estimates given in Table 6-8, although these estimates are based on the upper range of monitored vegetation levels. If consumable vegetables are harvested at the time that DFB is applied, levels on the vegetation are likely to be greater than the RRV for individuals who ingest only contaminated vegetables. The probability of this occurring, however, is questionable. In most parts of the country, DFB is applied in early spring, before local vegetables are ready for consumption. In such areas, the levels on vegetables at the time of harvesting will be far below the level of concern. In addition, this scenario does not explicitly consider the effects of washing or cooking on the levels of DFB in consumed vegetables.

From the single source estimates presented in Table 6-8, a variety of multiple source exposure scenarios can be constructed. The acute scenario presents an extreme example of risk. The major sources of risk are dermal contact with contaminated surfaces and the consumption of contaminated vegetation. As discussed above, the very high contribution from vegetable consumption may be implausible for most areas of the country. The contribution of contact with contaminated surfaces is far more plausible. The total of the component HQs is 7. This is equivalent to a daily dose of 0.14 mg/kg. Based on the most conservative interpretation of the available dose-response data, this exposure might increase methemoglobin levels by a factor of 2, from about 1% to 2%. The available data on methemoglobinemia in humans indicate that this would not lead to any clinically significant signs of toxicity.

The chronic scenario is intended to represent a more typical, although conservative, assessment of residual exposure levels over a prolonged period after treatment. None of the risks approach a level of concern. The total cancer risk, based on an upper estimate of the carcinogenic potency of DFB, is 1 in 2 million. More than 50% of this risk is associated with the consumption of contaminated vegetation.

6.5.5. Cumulative Effects

This risk assessment is based on single applications at the maximum allowable rate, 28 g a.i./acre. This approach is used to estimate maximum daily exposure and daily absorbed dose. Because the dispersal rate for DFB in the environment is relatively fast, multiple applications at lower rates per application will result in risks that are less than those associated with a single application at the maximum approved rate. Given the narrow range of application rates compared with the variabilities and uncertainties in the exposure and dose-response assessments, the risks of toxic effects associated with a single application at less than the maximum rate will be related directly to the application rate. Thus, an application at 14 g ai/acre will entail risks that are approximately one half of those expected at the maximum application rate. Two applications at 14 g ai/acre will entail risks that are intermediate between a single application at 14 g ai/acre and 28 g ai/acre. Since carcinogenic risks are calculated based on cumulative lifetime average dose, the risks of a single exposure at 28 g ai/acre is identical to two applications at 14 g ai/acre.

6.5.6. Connected Actions

Data indicating that exposure to DFB will affect human health responses to other agents used in gypsy moth control or to the gypsy moth itself were not located in the available literature. The most sensitive effects of DFB, methemoglobinemia, is not associated with any other agent used for gypsy moth control. Thus, in the absence of specific information on interactions between DFB and the other agents, it is not plausible to speculate that other program agents will interact with DFB or result in an additive response with DFB. In other words, the effects will be independent.

Exposure to other compounds in the environment that induce methemoglobinemia may lead to an additive effect. Individuals exposed to combustion smoke or carbon monoxide (that is, agents that do oxidative damage to blood) may be at increased risk of developing methemoglobinemia (Hoffman and Sauter 1989, Laney and Hoffman 1992). In addition, individuals exposed to high levels of nitrates, either in air or in water, will have increased levels of methemoglobin (Woebkenberg and others 1981) and may be at increased risks of exposure to compounds such as DFB.

6.5.7. Groups at Special Risk

Some individuals are born with a form of congenital methemoglobinemia and may be at increased risk of adverse effects to compounds that induce methemoglobinemia (Barretto and others 1984).

Infants less than 3 months old have lower levels of methemoglobin (cytochrome b5) reductase and higher levels of methemoglobin (1.32%), compared with older children or adults (Centa and others 1985, Khakoo and others 1993, Nilsson and others 1990). A similar pattern is seen in many species of mammals (Lo and Agar 1986). Some infants with an intolerance to cow's milk or soy protein exhibit methemoglobinemia (Murray and Christie 1993, Wirth and Vogel 1988). This condition may decrease the likelihood that those infants would be exposed to DFB through contaminated milk. Nonetheless, the infants may be at increased risk if exposed to any materials contaminated with DFB or any compound that induces methemoglobinemia.

Individuals with poor diets may be at increased risk to some chemicals. Based on a study in rats (Hagler and others 1981), iron deficiency leads to anemia but does not influence methemoglobin reductase activity. Thus, although individuals with poor nutritional status are generally a group for which there is particular concern, the available information does not support an increased concern for these individuals with respect to DFB exposure.

The most significant exposure scenarios for DFB involve dermal contact. Individuals with diseased or damaged skin may absorb chemicals such as DFB at a substantially greater rate, compared with the normal population. Those individuals may be at higher risk, but the magnitude of this risk will depend on the type and severity of skin damage.

Other individuals who may be considered at increased risk of exposure to chemicals in general include those with various disease conditions (for example, immunosuppressed or immunodeficient individuals, individuals with allergic conditions, and individuals with impaired liver, kidney, lung, or other organ functions), the very young or the very old, individuals with poor diets, pregnant women, or individuals suffering from MCS. Other than infants and individuals with damaged skin, there are no data to support an evaluation of the sensitivity of such individuals to DFB.

Table 6-1. Hematological effects of DFB in experimental mammals

Route	Exposure Dose/Duration	Effect	Reference
		Cats	
Oral	30, 70, 100, 300, 1,000 mg/kg bw/ 21 days	Dose-related elevation of methemoglobin in females at all dose levels and in males only at the three higher levels	Keet and others 1982
		Dogs [7%]	
Oral	2, 10, 50, 250 mg/kg/day/52 weeks	Increase in percent methemoglobin and sulfhemoglobin in three highest dose groups	Duphar 1985
Diet	10, 20, 40, 160 ppm/13 weeks	Methemoglobinemia at high dose group only	Chesterman 1974
		Mice [15%]	
Gavage	8, 40, 200, 1,000, 5,000 mg/kg bw/ 14 days	Methemoglobinemia and sulfhemoglobinemia and Heinz bodies at two highest dose levels	Keet 1977b
Diet	16, 50, 400, 2,000, 10,000, 50,000 ppm/13 weeks	Significant increase in percent methemoglobin and sulfhemoglobin in all dose groups; at >16 ppm, decreased hematocrit and erythrocyte counts and increased reticulocytes, platelet, and Heinz body counts; at two highest dose groups, increased alkaline phosphatase activity; hemosiderosis of the liver and spleen and extramedullary hematopoiesis	Burdock and others 1980a
Diet	80, 400, 2,000, 10,000, 50,000 ppm/14 weeks	Lower packed cell volume and red blood cell volume at all dose levels except the lowest; increased incidence of Heinz bodies and discoloration and enlargement of the spleen in all dose groups	Colley and others 1981

Table 6-1. Hematological effects of DFB in experimental mammals

Route	Exposure Dose/Duration	Effect	Reference
		Mice [15%]	
Diet	16, 80, 400, 2,000, 10,000 ppm/2 years (1.24, 6.4, 21.16, 163.29, 835.55 mg/kg/day)	Increased methemoglobinemia and sulfhemoglobin in four highest dose groups; Heinz bodies in three highest dose groups; increased extramedullary hematopoieses in liver at two highest dose groups and in spleen at the three highest dose groups; increased siderocytosis in spleen and of pigmented Kupffer cells in the liver at two highest dose groups Dose S-Hb M-Hb 0 0.1% 1.36 16 0.13% 1.38 80 0.34% 1.78 400 1.27% 2.96 2,000 3.45% 4.27 10,000 4.06% 5.92	Keet 1984b
Diet	16, 80, 400, 2,000, 10,000 ppm/2 years (1.44, 7.26, 35.38, 186.59, 958.51 mg/kg/day)	Increased sulfhemoglobin in four highest dose groups; increased methemoglobin in three highest dose groups; Heinz bodies in three highest dose groups Dose S-Hb M-Hb 0 0.12% 0.77 16 0.12% 0.89 80 0.22% 1.43 400 1.75% 2.76 2,000 3.94% 4.36 10,000 3.60% 5.40	Keet 1984b

Table 6-1. Hematological effects of DFB in experimental mammals

Route	Exposure Dose/Duration	Effect	Reference
		Rats [12%]	
Gavage	5,000 mg/kg bw/ 8 days	Marginal increase in methemoglobin and sulfhemoglobin on days 1 and 2 only; no change in number of Heinz bodies	Keet 1977a
Diet	800, 4,000, 20,000, 10,0000 ppm/4 weeks	Dose-related increase in methemoglobin and sulfhemoglobin in all treated groups, except for methemoglobin levels in females in low dose group; significant change in relative spleen weights	Palmer and others 1977
Oral	96.7 mg/kg/day/48 days	Decreased hemoglobin and neutrophil levels; increased hematocrit and basophil	Berberian and Enan 1989
Diet	160, 400, 2,000, 10,000, 50,000 ppm/13 weeks	Increased methemoglobin in all treated groups; increased sulfhemoglobin at $\geq$2,000 ppm; increased number of Heinz bodies at highest two dose levels. Increased spleen weights in females at all dose levels at 7 weeks but not at 13 weeks; hemosiderosis and congestion of the spleen and mild erythroid hyperplasia of the bone marrow	Burdock and others 1980b
Feeding	6.99, 28.36, 114.55, 453 mg/kg bw/104 weeks (156, 625, 2,500, 10,000 ppm)	Increase in absolute and relative methemoglobin and sulfhemoglobin in two highest dose groups	Keet 1984a
Feeding	9.23, 37.98, 153.96, 633.41 mg/kg bw/104 weeks (156, 625, 2,500, 10,000 ppm)	Increase in absolute methemoglobin and sulfhemoglobin in all dose groups. Increase in relative methemoglobin and sulfhemoglobin in three highest dose groups	Keet 1984a

Table 6-1. Hematological effects of DFB in experimental mammals

Route	Exposure Dose/Duration	Effect	Reference
		Rabbits [7%]	
Diet	640 ppm/ 8 days	Methemoglobin increased from day 5; higher sulfhemoglobin within 5 hours	Keet 1977c
		Sheep [5%]	
Diet	500, 2,500, 10,000 ppm/13 weeks	Increase in sulfhemoglobin and methemoglobin in high dose group at 4 and 8 weeks; significant increase in sulfhemoglobin in all treated groups at 13 weeks	Ross and others 1977

Note: The value in brackets after the species name is the daily food consumption as a percent of body weight from U.S. EPA (1987a).

Table 6-2. Effects of DFB on reproductive function and reproductive tissue

Species/ Age at Start	Dose/ Duration	Effect	Reference
White Leghorn hens/42 weeks	10, 50, 100, 500 ppm in food for 8 weeks	No effects on food consumption, body weight, egg production, egg weight, egg shell thickness, fertility, hatchability, or progeny performance; increased food consumption in high dose group	Cecil and others 1981
White Leghorn hens/28 weeks	10, 50, 100, 500 ppm in food for 8 weeks	No effects on food consumption, body weight, egg production, egg weight, egg shell thickness, fertility, hatchability, or progeny performance; increased food consumption in all dose groups; decrease in weight of male progeny (50 ppm dose group only) 8 weeks after birth; increase in weight of female progeny (all dose groups) at 8 weeks after birth; increase significant only in high dose group	
White Leghorns and Black Sexlinked Cross/ egg laying	10 ppm for 15 weeks	Slight decrease in food consumption for Black Sexlinked Cross; no effects on weight gain, egg production, fertility of eggs, or hatchability	Miller and others 1976
Male Holstein cattle/3 days	1–2.8 mg/kg/day/4 months to 1.5 years	No effect on testosterone, libido, or sperm motility; no histopathological effects on liver, lung, kidney, or spleen tissues	Miller and others 1979
Chickens/ 1 day	2.5, 25, 250 ppm/ throughout growth and through one laying cycle	No effect on egg production, egg weight, eggshell weight, fertility, hatchability, or progeny, body weight of progeny measured at 1 and 2 weeks after birth	Kubena 1982, Kubena and Witzel 1980

Table 6-3. Selected monitoring studies on diflubenzuron in water

Formulation	Application Rate (g/acre)	Time after Application	Level (μg/L)	Reference
25W in pastures (half-time = 0.7 days)	9–45	1 hour	1.5–32	Schaefer and Dupras 1976[a]
		1 day	1.3–8.2	
		2 days	1.3–5.4	
		3 days	1.0–2.0	
Granules in pastures (half-time = 1.5 days)	10–14.5	1 hour	7–24	
		1 day	4.5	
Liquid in dairy drain (half-time = 0.2 days)	18–50	1 hour	6.3–1,390	
		1 day	2.2–6.9	
		2 days	1.6–2.4	
25W in ponds (half-time = 2.7 days)	28	1 hour	5.9–13.8	Sundaram and others 1991[b]
		1 day	2.8–4.3	
		2 days	2.1–3.4	
25W in streams		1 hour	1.6–3.3	
		1 day	0.13	
25W in stream	27	1 hour	0.11	Jones and Kochenderfer 1988
		1.5 hours	2.1[c]	
		2 days	0.03	
Run-off (half-time = 58 days)	30	1 day	5	Mutanen and others 1988[d]
		6 days	1	
		61 days	0.1	
Groundwater		1 and 7 days	0.1	
		26 days	0.2	

[a]Summarized monitored levels exclude samples below the limit of detection. From Table VII in Schaefer and Dupras 1976.

[b]From Table 3 in Sundaram and others 1991.

[c]After 0.5 inches of rain.

[d]Neither 4-chloroaniline nor 4-chlorophenylurea were found (detection level = 0.2 μg/L).

Table 6-4. Bioconcentration of DFB and 4-chloroaniline by bluegill sunfish

Time After Treatment	DFB			4-Chloroaniline		
	Water[a]	Fish[b]	BCF[c]	Water[a]	Fish[b]	BCF[c]
3 hours	1.15	119	103	ND[d]	0.8	NA
5 days	4.9	400	82	0.30	1.3	4.3
12 days	1.8	175	100	0.10	1.0	10
19 days	1.3	72	55	0.15	1.1	7.3

Source: Schaefer and others 1980

NA = Not applicable

[a]Concentration in water, μg/L.

[b]Concentration in fish, μg/kg.

[c]Bioconcentration Factor = concentration in fish ÷ concentration in water.

[d]Detection limit for 4-chloroaniline = 0.1 μg/L.

Table 6-5. Dose-response relationships for methemoglobin formation in various experimental mammals

Species	Duration of Exposure (weeks)	MetHb in Controls (%)	NOAELs (mg/kg/day)	LOAEL[a] (mg/kg/day)	MetHb at LOAEL[a] (%)
Cat	3	0.68	30, 100, 300	1,000	10.13
Mouse	14	0.75	10, 52, 260	1,250	4.14
Rat	14	1.0	12, 30, 150	800	3.43
Dog	13	1.3	2, 10, 50	250	3.8
Sheep	13	1.0	25, 125	500	2.0

Source: (Keet and others 1982)

[a]LOAEL defined as percent methemoglobin significantly ($p < 0.05$) greater than control level. No overt toxic effects observed in any species.

Table 6-6. Levels of methemoglobin in humans

Level (%)	Characterization	Reference
0.67	Nonsmokers, England	Borland and others 1985
0.6	Smokers, England	
0.59	Nonsmokers, Italy	Imbriani and others 1987
0.63	Smokers, Italy	
3.8	Nonsmokers, Rural USA	Woebkenberg and others 1981
1.3	Nonsmoker, Urban USA	
3.6	Smokers, Rural USA	
2.2	Smokers, Urban USA	
<1.0	Normal	Das Gupta and others 1980
35.0	Asymptomatic individual with congenital methemoglobinemia	
18-36	Infants hospitalized with methemoglobinemia	Centa and others 1985
24.8	28-year-old with cyanosis and shortness of breath	Laney and Hoffman 1992
35	4-week-old infant with moderate diarrhea and acidosis	Wirth and Vogel 1988
53.5	Cyanosis and lethargy; decreased respiratory rate	Daly and others 1983

Table 6-7. Summary of risk characterization for workers using Diflubenzuron

Scenario/Group	Daily Dose (mg/kg)	Hazard Quotient	Upper Limit of Cancer Risk
Aerial Spray Workers, Routine			
Pilots	$1 \cdot 10^{-4}$	0.005	$3 \cdot 10^{-9}$
Mixers/loaders	$2 \cdot 10^{-4}$	0.01	$6 \cdot 10^{-9}$
Flagmen	$3 \cdot 10^{-6}$	0.002	$8 \cdot 10^{-11}$
Aerial Spray Workers, Upper Range			
Pilots	$2 \cdot 10^{-3}$	0.1	NA
Mixers/loaders	$6 \cdot 10^{-2}$	3.0	NA
Flagmen	$8 \cdot 10^{-5}$	0.004	NA
Ground Spray Workers			
Average	$1 \cdot 10^{-3}$	0.05	$3 \cdot 10^{-8}$
Upper range	5.10^{-2}	3.0	NA
Accidents			
Immersion - hands, 1 minute	$3 \cdot 10^{-7}$	0.00001	
Saturated clothing - hands, 1 hour	$2 \cdot 10^{-5}$	0.0008	NA
Spill, routine	$9 \cdot 10^{-3}$	0.5	
Spill, extreme	$8 \cdot 10^{-1}$	40	

RRV = 0.02 mg/kg
Cancer Potency of DFB:
Best Estimate = 0.0001 $(mg/kg/day)^{-1}$
Upper Range = 0.0004 $(mg/kg/day)^{-1}$

Duration of Exposure:
For accidents = risk for each accident
1 minute for immersion
1 hour for saturated clothing
1 hour to 1 day for spill
Factor on dose for cancer risk: $1 \div (365 \cdot 70) = 0.00004$
For all others = 3 months/year for 20 years
Factor on dose for cancer risk: $(3 \div 12) \cdot (20 \div 70) = 0.05$

Table 6-8. Summary of risk characterization for the public exposed to Diflubenzuron

Scenario/Group	Daily Dose (mg/kg)	Hazard Quotient	Upper Limit of Cancer Risk
Dermal Exposures			
Direct Spray			
Routine	$2 \cdot 10^{-5}$	0.001	$3 \cdot 10^{-13}$
Extreme	$1 \cdot 10^{-3}$	0.05	$1 \cdot 10^{-11}$
Aircraft load ejection			
Routine	$6 \cdot 10^{-3}$	0.3	$6 \cdot 10^{-11}$
Extreme	$2 \cdot 10^{-2}$	**1.0**	$3 \cdot 10^{-10}$
Saturated clothing	$4 \cdot 10^{-4}$	0.01	$6 \cdot 10^{-12}$
Contaminated surfaces			
Immediately after	$4 \cdot 10^{-3}$	0.2	$5 \cdot 10^{-11}$
1 week after	$6 \cdot 10^{-5}$	0.003	$2 \cdot 10^{-11}$
>2 weeks after	0	0	0
Oral - Water			
Direct spray			
DFB	$4 \cdot 10^{-3}$	0.2	$6 \cdot 10^{-11}$
4-Chloroaniline	$4 \cdot 10^{-4}$	0.1	$2 \cdot 10^{-10}$
Total		0.3	$3 \cdot 10^{-10}$
Ambient water			
Initial			
DFB	$1 \cdot 10^{-3}$	0.005	
4-Chloroaniline	$1 \cdot 10^{-4}$	0.03	
Total		0.04	$3 \cdot 10^{-8}$
> 2 weeks			
DFB	$1 \cdot 10^{-4}$	0.0005	
4-Chloroaniline	$1 \cdot 10^{-5}$	0.0003	
Total		0.0008	

Table 6-8. Summary of risk characterization for the public exposed to Diflubenzuron

Scenario/Group	Daily Dose (mg/kg)	Hazard Quotient	Upper Limit of Cancer Risk
Contaminated fish			
Initial			
DFB	$2 \cdot 10^{-3}$	0.1	
4-Chloroaniline	$2 \cdot 10^{-4}$	0.05	
Total		0.2	
2 weeks - 1 month			
DFB	$2 \cdot 10^{-4}$	0.01	
4-Chloroaniline	$2 \cdot 10^{-5}$	0.005	$6 \cdot 10^{-8}$
Total		0.02	
> 1 month			
DFB	$2 \cdot 10^{-5}$	0.001	
4-Chloroaniline	$2 \cdot 10^{-6}$	0.0005	
Total		0.002	
Contaminated vegetation			
Initial levels			
Average	$4 \cdot 10^{-2}$	2	NA
Maximum	$1 \cdot 10^{-1}$	5	
Routine consumption			
Average	$3 \cdot 10^{-3}$	0.2	NA
Maximum	$1 \cdot 10^{-2}$	0.5	
Prolonged levels			
Routine	$8 \cdot 10^{-6}$	0.0005	$3 \cdot 10^{-9}$
Extreme	$2 \cdot 10^{-4}$	0.01	$7 \cdot 10^{-8}$

Table 6-8. Summary of risk characterization for the public exposed to Diflubenzuron

Scenario/Group	Daily Dose (mg/kg)	Hazard Quotient	Upper Limit of Cancer Risk
Contaminated animals			
Game species or cattle	0	0	0
Maximum in cows' milk	$2 \cdot 10^{-2}$	**1.0**	$3 \cdot 10^{-10}$
Typical in cows' milk	$5 \cdot 10^{-5}$	0.003	$2 \cdot 10^{-8}$
Birds	$2 \cdot 10^{-4}$	0.01	$3 \cdot 10^{-12}$
Inhalation			
Immediately after spray	$5 \cdot 10^{-6}$	0.0003	$9 \cdot 10^{-14}$
Multiple Route/Source Scenarios			
Acute, extreme			
Direct spray		0.05	
Contaminated surfaces		0.2	
Water consumption		0.3	
Fish consumption		0.2	NA
Vegetation consumption		5	
Cows' milk		1	
Total		7	
Chronic, typical			
Ambient water consumption		0.0008	$3 \cdot 10^{-8}$
Fish consumption		0.002	$6 \cdot 10^{-8}$
Vegetation consumption		0.01	$7 \cdot 10^{-8}$
Cows' milk		0.003	$2 \cdot 10^{-8}$
Total		0.01	$2 \cdot 10^{-7}$

RRV of DFB = 0.02 mg/kg
RRV of 4-Chloroaniline = 0.004 mg/kg
Cancer Potency of DFB:
Best Estimate = $1 \cdot 10^{-4}$ $(mg/kg/day)^{-1}$
Upper Range = $4 \cdot 10^{-4}$ $(mg/kg/day)^{-1}$
Cancer Potency of 4-Chloroaniline: $1 \cdot 10^{-2}$ $(mg/kg/day)^{-1}$
Duration of Exposure for Cancer Risk:
1 spray program/year, 1 application/program at maximum application rate, for 70 years See text for additional details

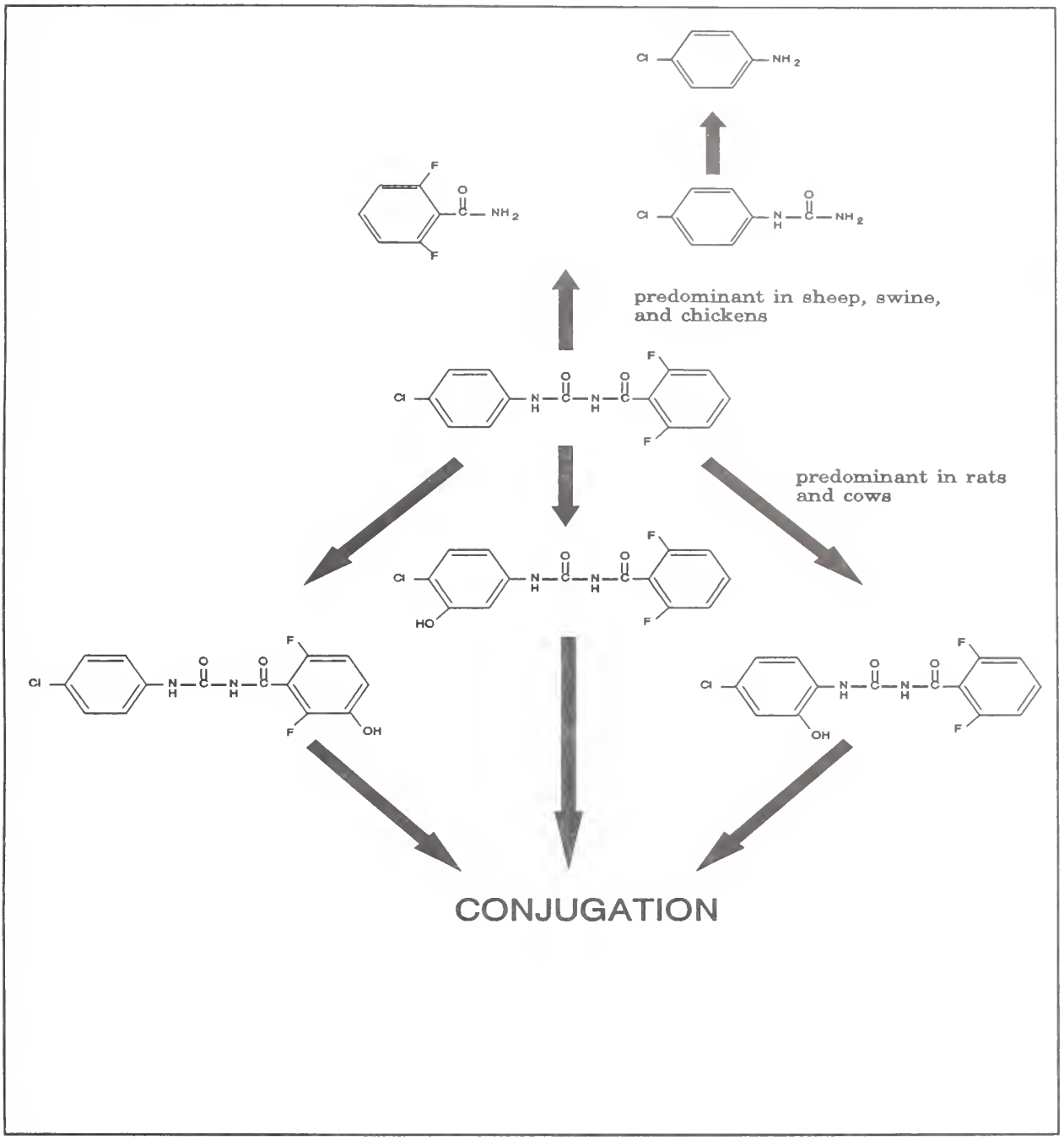


Figure 6-1. Mammalian Metabolism of DFB (modified from WHO 1985). The metabolism of DFB has been characterized in chickens and several mammalian species. In sheep, swine, and chickens, the predominant pathway is breaking of the carbon-nitrogen bridge. In rats and cows, hydroxylation of either aromatic ring followed by biliary elimination is the more common pathway. No information is available regarding metabolism in humans. The structure and names for most scission products of DFB in mammals and other organisms are given in Figure 6-2.

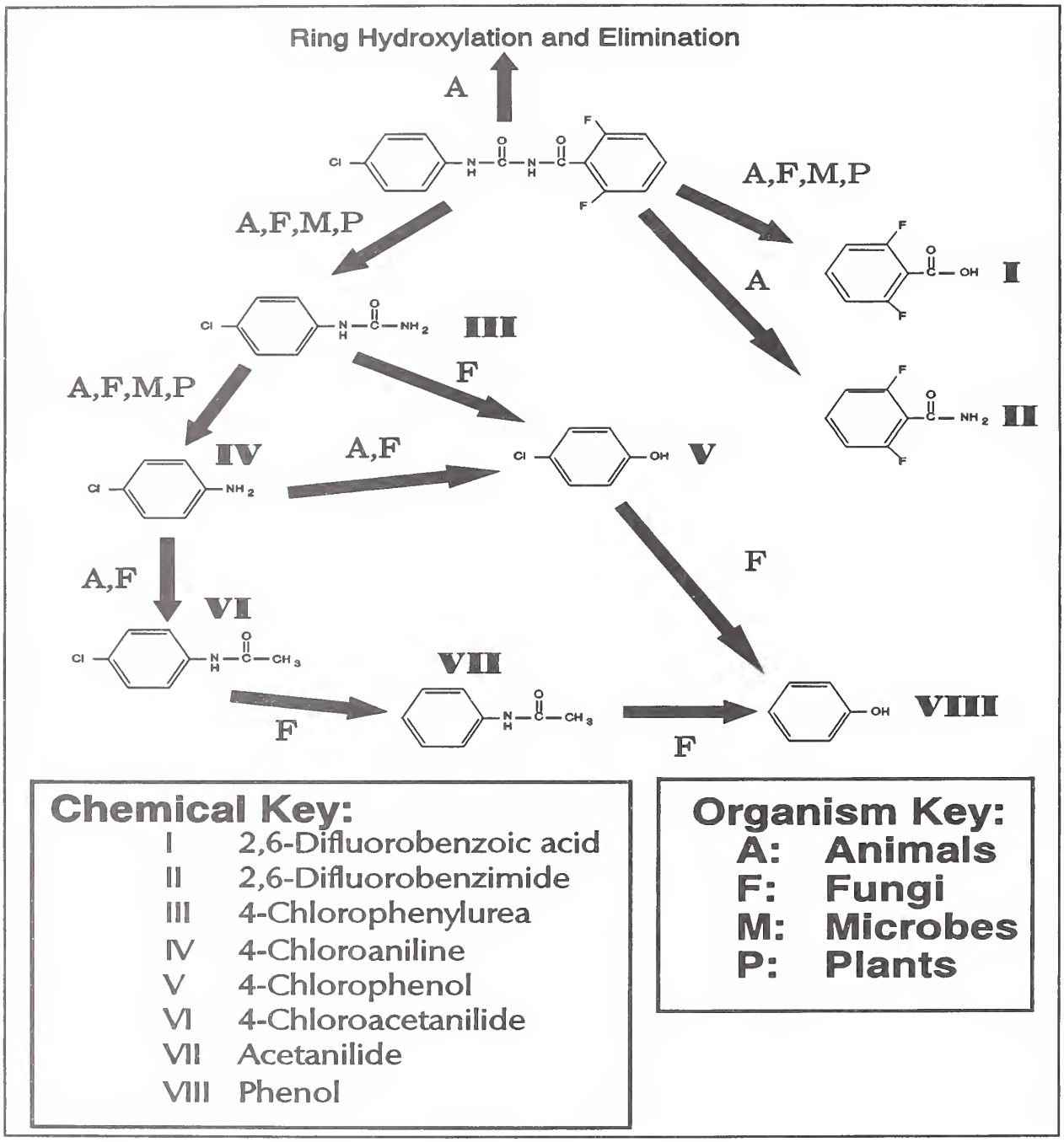


Figure 6-2. Overview of the Metabolism of Dimilin by Various Organisms [modified from Figure 2 in Mian and Mulla (1984, p. 82)]. Various organisms are able to cleave the carbon-nitrogen bridge of DFB. The formation of 4-chloroaniline is important to this risk assessment because of the potential carcinogenicity of this compound.

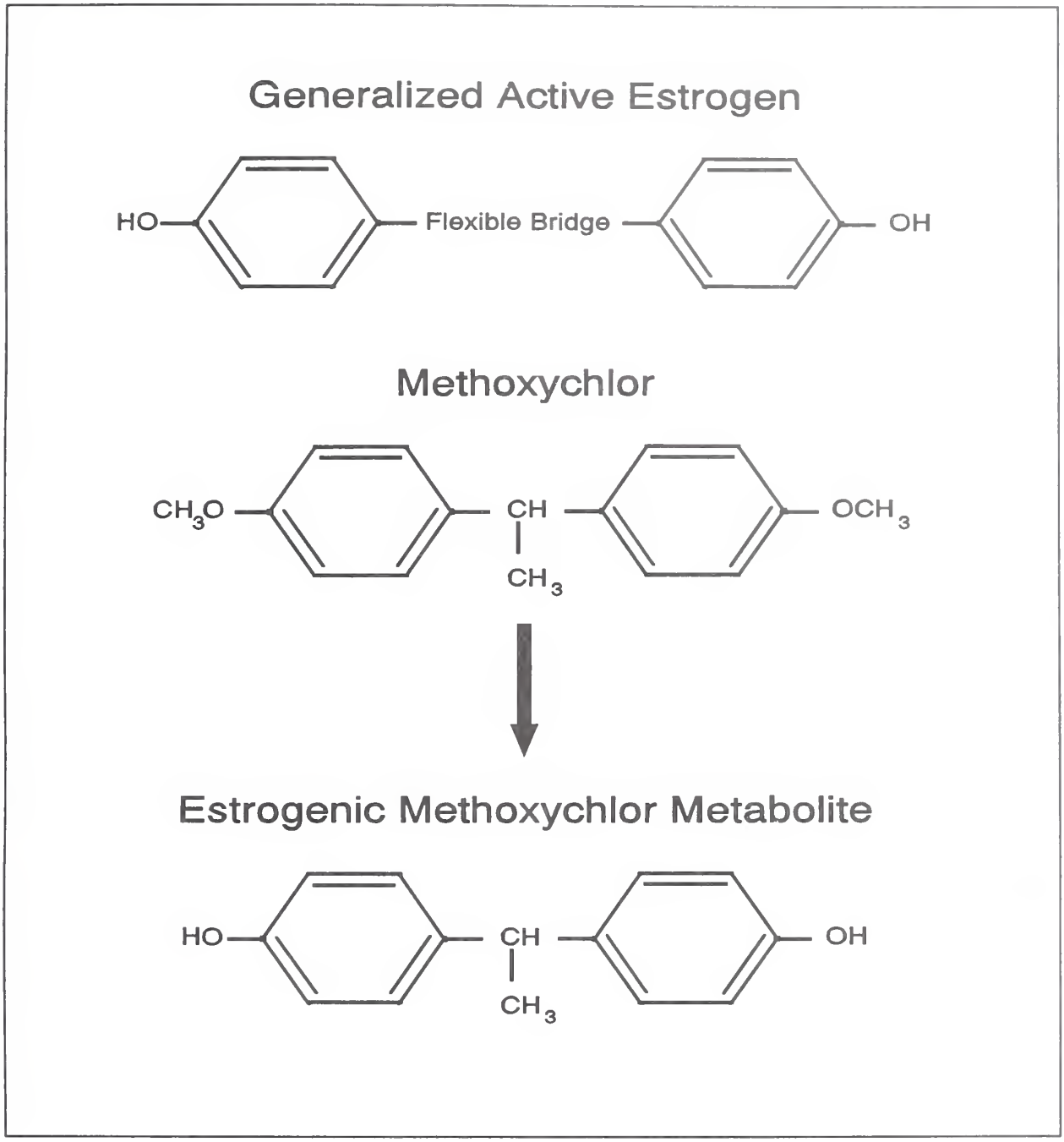


Figure 6-3. Qualitative Structure-Activity Relationships for Nonsteroidal Estrogenic Compounds. Generally, nonsteroidal estrogenic compounds, such as methoxychlor, are characterized by at least two aromatic rings separated by a flexible aliphatic bond with hydroxyl substitution in both para positions on the aromatic rings. Estrogenic activity involves metabolism to a para-biphenolic derivative (hydroxyl groups on both aromatic rings in the carbons opposite to the bridge that connects the aromatic rings). DFB is not likely to undergo such activation.

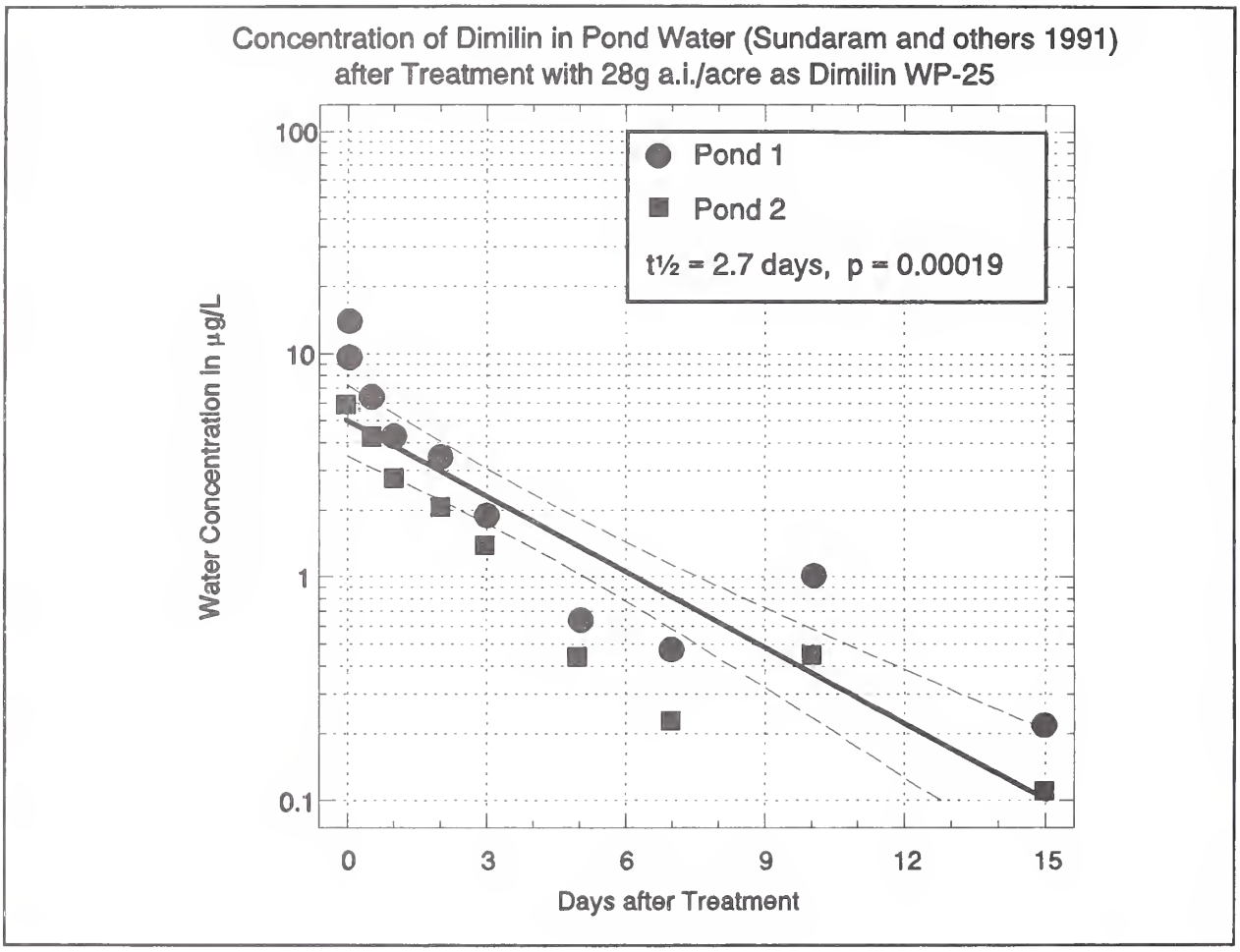


Figure 6-4. Water Levels of Dimilin (WP-25) in Two Ponds After Aerial Application of 28 g/acre (Sundaram and others 1991). The half-time for DFB based on the combined data for both ponds is approximately 2.7 days. Although the simple exponential decay model adequately fits the data, the pattern of DFB loss appears to be more complex than first order. This is particularly evident for Pond 1.

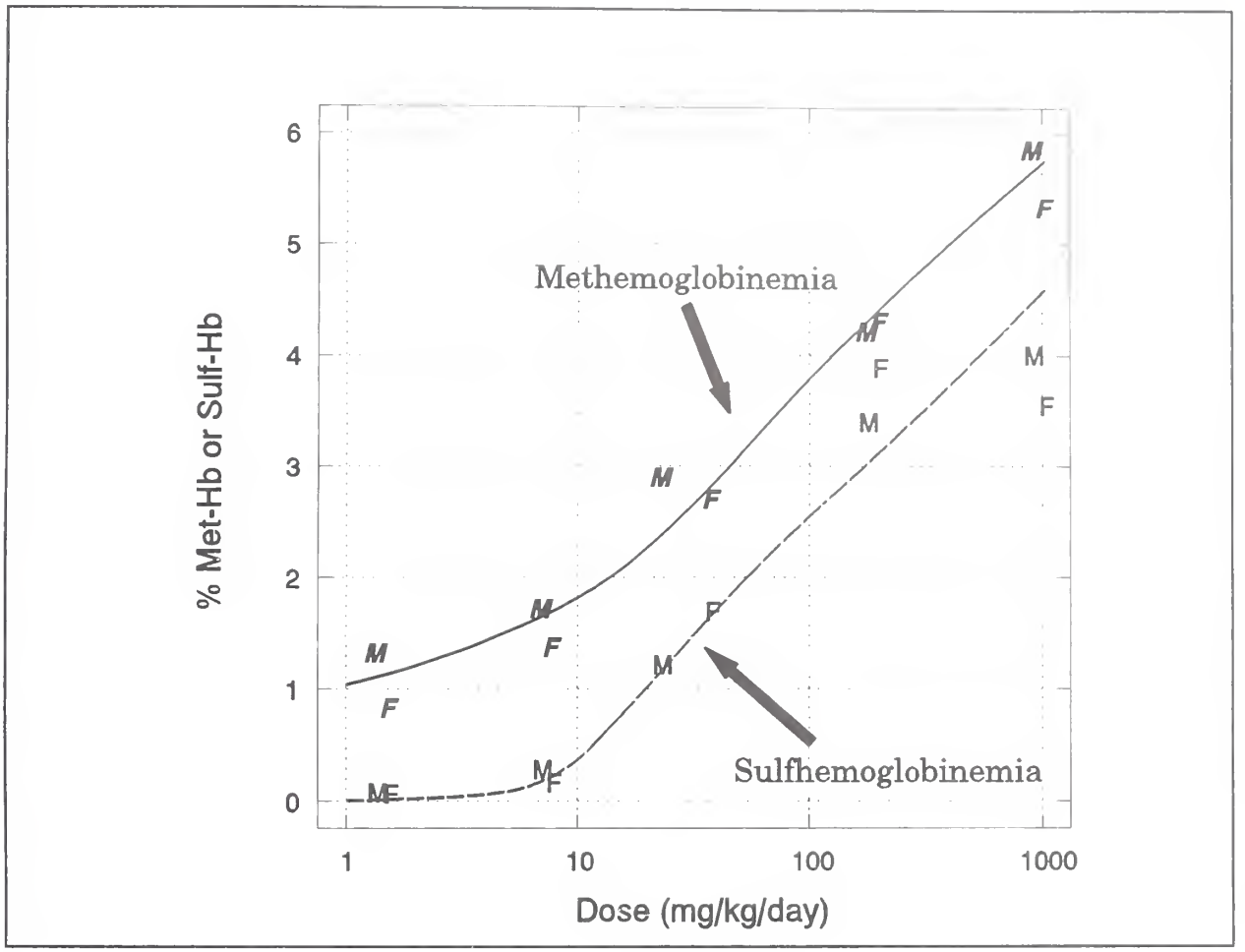
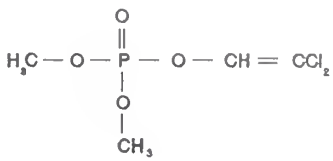


Figure 6-5. Dose-Response Relationships for the Hematopoietic Effects of DFB in Male (M) and Female (F) Mice After 2-Year Dietary Exposures. In assessing risks above the RRV, the most important issue is the relationship of the formation of methemoglobin and sulfhemoglobin to clinically significant adverse effects. In this study on mice, doses of up to 1,000 mg/kg increased levels of methemoglobin to approximately 6%. This effect is not likely to be clinically significant in humans (see Table 6-6).

7. DDVP

7.1. Program Description

DDVP (2,2-dichloroethenyl dimethyl ester phosphoric acid), also known as Dichlorvos, is a contact and stomach organophosphate insecticide (Gallo and Lawryk 1991, IARC 1991). The molecular structure of DDVP is:



DDVP is registered with the U.S. EPA and manufactured by AMVAC Chemical Corporation. DDVP is undergoing re-registration (AMVAC 1993). Although DDVP has been registered for crop use, that use is not supported in the AMVAC re-registration effort.

DDVP is used by the USDA as an insecticide in large capacity pheromone traps for the gypsy moth. These traps are used to monitor gypsy moth populations. In the gypsy moth programs, the Vaportape II strip is contained in the milk carton trap together with a carrier containing Disparlure. During fiscal year 1994 (that is, October 1, 1993 to September 30, 1994) the USDA ordered 33,750 milk carton traps, which is equivalent to an annual use of approximately 20 kg DDVP

$$0.59 \text{ g/trap} \cdot 33{,}750 \text{ traps/year} \div 1{,}000 \text{ g/kg} = 19.9 \text{ kg/year}$$

or 44 pounds (20 kg · 2.2 pounds/kg).

The milk carton traps containing the DDVP strips are placed in selected areas to monitor gypsy moth infestations. The populations of concern to the human health risk assessment are limited to individuals who might come into contact with the DDVP strip placed in the field and workers who use the strip in trap assembly.

As discussed in the exposure assessment (section 7.3), the nature of the exposures involving the general public may be extremely variable, and it is unlikely that significant exposures will occur under normal circumstances. For workers, the nature of exposure to DDVP depends on program handling practices, which vary from state to state. Table 7-1 summarizes worker practices for five states. In most cases, dermal and inhalation exposure will be minimal, provided that recommended work practices are followed. In four of the five states included in Table 7-1, inhalation exposure will be minimal because strip installation takes place outdoors, at the trap placement site. In Ohio, traps may be assembled the day before placement. Even so, the workers are instructed to assemble the traps only in

a well-ventilated area, and the traps are sealed in plastic bags after assembly and prior to transport. Dermal exposure is also likely to be minimal. In four of the five states included in Table 7-1, workers are given plastic gloves and instructed to use them. Although workers in Michigan are not provided with gloves, they are instructed to touch only the plastic wrapper in which the DDVP strip is shipped.

7.2. Hazard Identification

7.2.1. Overview

Exposure to DDVP is associated with adverse health effects in humans and laboratory animals. The compound is known to inhibit acetylcholinesterase (AChE), an enzyme involved in the regulation of the nervous system. Sufficiently high levels of AChE inhibition cause serious toxic effects including death. AChE inhibition is the most sensitive effect of clear clinical significance. Other effects, such as those on reproductive function, occur only at much higher doses and over longer periods of exposure than those anticipated in this risk assessment. Consequently, the neurological effects of DDVP are the main focus of this risk assessment. DDVP has been shown to cause cancer in laboratory animals, and some studies suggest that DDVP causes various forms of cancer in humans. Although the methods used to estimate cancer risk from short-term exposures, such as those used in this assessment, are at best crude approximations, these risks also are considered.

7.2.2. Commercial Formulation: Impurities and Inerts

The DDVP is formulated as Vaportape II, produced by Hercon Environmental Company (Hercon 1993). Vaportape II is distributed in packages of 50 strips, each of which comes in a protective pouch. Each strip consists of a 1 x 4 inch red, multi-layered polyvinyl chloride (PVC) tape containing 590 mg of DDVP. The average thickness of the strip is 67.5 mil with a range of 65–70 mil or 0.0675 inches with a range of 0.065–0.07 inches (Hercon 1994).

The label specifies that in addition to DDVP, each strip contains 0.75% compounds that are related to DDVP. Further details are not provided on the label; nonetheless the impurities in commercial DDVP have been characterized (Gillett and others 1972a, IARC 1991). The impurities include: Dipterex (O,O-dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate); O,O-dimethyl 2-chlorovinyl phosphate; O,O-dimethyl methylphosphonate; O,O,O-trimethyl phosphate; and trichloroacetaldehyde. These impurities are known to be or are likely to be toxic (Gillett and others 1972a, WHO 1989). These impurities are encompassed in the risk assessment because the dose-response assessment is based on studies that used commercial grade DDVP. Consequently, the results of these studies are directly applicable to this risk assessment.

7.2.3. Cholinergic Effects

Like all organophosphate insecticides, DDVP combines with and inhibits AChE. The biochemical basis for the toxic effects of DDVP is related to the normal function of AChE. In the cholinergic system, neural impulses are transmitted between nerve cells or between nerve cells and an effector cell (such as a muscle cell) by the acetylcholine. When the acetylcholine reaches a certain level, the receptor cell is stimulated. Normally, the acetylcholine is then rapidly degraded to inactive agents (acetic acid and choline) by AChE. When AChE activity is inhibited by organophosphates, acetylcholine persists and continues to accumulate at the synapse (the space between the two cells). Initially, this accumulation causes continuous stimulation of the cholinergic system, which may be followed by paralysis because of nerve cell fatigue (ATSDR 1993). Depending on the dose and duration of exposure, and the resulting degree of AChE inhibition, organophosphate insecticides may induce a broad spectrum of clinical effects (Table 7-2).

The cholinergic effects of DDVP are well documented in studies involving humans, wildlife, and experimental mammals (Gillett and others 1972a and 1972b, IARC 1979 and 1991, WHO 1989). As discussed in the dose-response assessment (section 7.4), DDVP also inhibits other cholinesterases outside of the nervous system and induces clinical signs of intoxication consistent with those of AChE inhibition (Table 7-2).

Oral LD_{50} values for experimental mammals range from 25 to 300 mg/kg (Gaines 1969, Jones and others 1968, Muller 1970, Wagner and Johnson 1970). All of these studies are based on the administration of DDVP in vehicles that do not inhibit absorption. The containment of DDVP in a slow-release vehicle, such as PVC, will inhibit acute toxic effects. The kinetics of DDVP release from PVC were investigated in a study in which DDVP was incorporated into PVC at 20% (w/w) (Slomka and Hine 1981). The PVC was extruded, cut into pellets, and encased in a hard gelatin capsule. The release of DDVP from the capsules was assayed in vitro using an artificial gastric fluid and in vivo in swine and humans. The release rates in the three assays were comparable; approximately 30% was released in the first 24 hours, and the subsequent release appeared to follow a first order function with a release rate of approximately 0.1 day^{-1}. The effect of PVC encapsulation on the toxicity of DDVP has been quantified in parallel assays (Stanton and others 1979), in which DDVP (undiluted technical grade) and DDVP (impregnated in PVC) were administered to groups of young swine. For the technical grade liquid formulation, the LD_{50} was 157 (113–227) mg/kg; for the PVC formulation, no deaths occurred at doses of 1,000 mg/kg or less.

One of the major diagnostic tools and measures of exposure to DDVP and other organophosphate insecticides is the determination of cholinesterase inhibition (ChE) in various tissues, most often red blood cells (RBC) and plasma (Ecobichon 1991, Gallo and Lawryk 1991, Murphy 1980). Plasma cholinesterase, sometimes referred to as pseudocholinesterase, is produced by the liver and differs from AChE in structure and substrates (ATSDR 1993). The normal physiological role of plasma ChE is not known.

Inhibition of RBC AChE is generally regarded as a more clinically significant index of organophosphate exposure, compared with inhibition of plasma AChE.

Normal ChE activities vary by a factor of 4 among individuals. Consequently, interpreting differences between cholinesterase levels in exposed groups and control groups is more difficult than interpreting differences between individual ChE levels before and after exposure (ATSDR 1993). All of the human and animal studies on PVC-DDVP formulations report AChE levels using the method involving treated groups and control groups. For all of the human studies on DDVP (Cervoni and others 1969, Hine and Slomka 1970, Pena-Chavarria and others 1969, Slomka and Hine 1981), the interpretation is further complicated because ChE levels are reported as ranges of inhibition, rather than mean values with standard errors. Consequently, as discussed in the dose-response assessment (section 7.4), the determination of NOAELs and AELs based on inhibition of RBC AChE is confounded.

As discussed in the general literature and illustrated in the human studies on DDVP, inhibition of ChE in plasma and blood is not associated, necessarily, with clinically significant adverse effects (Gage 1967, Wills 1972). Generally, 50% inhibition of normal ChE levels (post exposure activity divided by pre-exposure activity) is regarded as clinically significant (ATSDR 1993).

A significant characteristic of some organophosphate insecticides is that the reversibility of enzyme inhibition is slow (Murphy 1980). Relatively little information is available on the reversibility of inhibition due to DDVP. There is one case report indicating substantial inhibition of ChE, 36% of normal, in an individual exposed to DDVP 3 days before the assay of ChE activity (Bisby and Simpson 1975).

Some organophosphorus compounds, such as trichlorfon and merphos, cause delayed neuropathy in humans. Clinical manifestations include calf pain or tingling in the hands and feet. These effects usually appear 7–14 days after exposure, when signs of cholinergic toxicity have resolved and can persist for weeks or years (ATSDR 1993). There are several studies that demonstrate that DDVP does not induce delayed neuropathy (WHO 1989). Nonetheless, when very high doses of DDVP were administered to hens, the compound severely inhibited brain and spinal cord esterases, leading to clinical neuropathy (Johnson 1978 and 1981).

7.2.4. Mutagenicity and Carcinogenicity

DDVP has been tested extensively for mutagenicity, and the results of the tests are available in data reviews (IARC 1979 and 1991, Ramel and others 1980). Mutagenic effects as well as covalent binding to RNA and DNA have been demonstrated in bacterial systems. Generally, mutagenicity is decreased by the presence of liver microsomal preparations.

DDVP produced positive results in mammalian bioassays for carcinogenicity. A cancer bioassay was conducted in which male and female mice were given gavage doses of DDVP (NCI 1977). The doses levels were 10 and 20 mg/kg for males and 20 and 40 mg/kg for females. There was a significant dose-related increase in squamous-cell papillomas of the forestomach in both sexes. In females at the high dose level, the incidence of squamous-cell carcinomas was significantly greater than in the control group ($p=0.004$). In the same study, male rats were given 4 mg/kg/day DDVP by gavage and female rats were given 8 mg/kg/day. A significant ($p<0.001$) dose-related increase in the incidence of acinar-cell adenomas of the pancreas was observed in the males. The increased incidence of fibroadenomas and adenomas of the mammary gland was significant ($p=0.028$) in the females. Two other bioassays conducted on the carcinogenicity of DDVP after oral exposure are reviewed by IARC (1991). Neither study indicated significant evidence of carcinogenicity.

The only study available regarding the carcinogenicity of DDVP with respect to inhalation exposure was conducted by Blair and others (1976). Male and female rats were exposed to 0, 0.05, 0.5 and 5 mg/m^3 DDVP for 104 weeks. No significant increase of tumor incidence was observed; however, only 20%–32% of the male rats and 22%–38% of the female rats were necropsied, limiting the usefulness of this study for assessing the potential carcinogenicity of DDVP with respect to inhalation exposure (IARC 1991).

As reported in a series of case studies, four children with aplastic anemia and one child with acute lymphoblastic leukemia were exposed to DDVP in the course of normal household use (Reeves and others 1981). IARC reviewed the study and concluded that it was not adequate for determining the potential human carcinogenicity of DDVP (IARC 1991). More recent studies have found positive associations between childhood brain cancer and exposures to DDVP during childhood or during gestation (Davis and others 1992 and 1993).

Based on the available data, DDVP is classified as a Class 2B carcinogen (IARC 1991, U.S. EPA 1994a); DDVP is possibly carcinogenic to humans (IARC 1991) or is a probable human carcinogen (U.S. EPA 1994a). This classification is given because there are inadequate data to assess the potential carcinogenicity of DDVP in humans but adequate data to indicate that DDVP is carcinogenic to experimental animals. Neither the IARC nor the U.S. EPA classification reflects the data from the studies by Davis and others, discussed above.

7.2.5. Reproductive and Teratogenic Effects

According to some studies, exposure to DDVP caused reproductive and teratogenic effects in laboratory animals; on the other hand, there are several breeding studies in which no adverse reproductive or teratogenic effects were observed in rabbits, swine, or experimental mammals after exposure to DDVP. In a study in which female rats were given intraperitoneal injections of 15 mg/kg DDVP on day 11 of gestation, herniation of the umbilical cord was observed in 3 of 41 offspring from the treated group (Kimbrough and

Gaines 1968). The effect was not observed in offspring from the control group. When rabbits were treated with 6 mg/kg DDVP during the last 10 days of gestation and the brain tissue of the offspring was examined by electron microscopy, there was an incidence of immaturity or delay in brain development that was not apparent in the offspring of the untreated rabbits (Dambska and others 1979). The method of dosing the animals is not specified in this study.

Adverse testicular effects were observed in mice after chronic exposure to average daily doses of 0, 58, or 94.8 mg/kg/day DDVP in drinking water (AMVAC 1989). There was a dose-related decrease in the absolute and relative weight of the testes, and testicular atrophy was increased at the high dose.

Two reproduction studies investigated exposure to PVC-DDVP formulations. In one of the studies, swine were exposed to 5 or 25 mg/kg/day PVC-DDVP during the last 30 days of gestation (Stanton and others 1979). Sows and fetuses were monitored for changes in ChE. Both plasma and RBC ChE were inhibited in sows, and brain AChE was increased in fetuses. In a separate experiment conducted by these investigators, there were no significant effects on reproductive capacity in sows treated with 25 mg/kg/day DDVP during the last 30 days of gestation. In an abstract, Vogin (1971) reports that no adverse effects on reproduction or developmental parameters were observed in dams exposed to PVC-DDVP concentrations that did not cause maternal toxicity. Maternal toxicity was evident in dams treated with 34 mg/kg.

7.2.6. Dermal Irritation and Sensitization

The available human data supported by studies on experimental animals suggest that DDVP may cause skin irritation and/or allergic reactions. In New Zealand white rabbits, the application of an aqueous solution of 5%–20% DDVP caused relatively severe irritation (Arimatsu and others 1977). In a skin sensitization assay, 1% DDVP in olive oil induced no visible effects in male albino guinea pigs (Kodama 1968). In a guinea pig assay for allergenicity, 35% of the tested guinea pigs had a positive response to a 0.5% solution of DDVP (Fujita 1985).

Human data regarding the dermal effects of DDVP are relatively sparse but generally support the animal studies. In a case report, relatively severe contact dermatitis developed in an adult male after a 1% solution of DDVP leaked onto his skin (Bisby and Simpson 1975). This effect was accompanied by signs of cholinergic toxicity, including fatigue, dizziness, and labored respiration. Table 7-3 summarizes general public exposure to DDVP pest strips, which involved predominantly dermal contact with the insecticide (U.S. EPA 1981). The usefulness of these reports is limited because the descriptions of the exposures and responses are brief and often incomplete. Nonetheless, of the eight incidents reported, four suggest either an irritant or allergic response. In a study regarding the effects of dermal exposure to

a DDVP pest strip on AChE activity, no dermal effects were noted in 21 individuals in which dermal contact with the strip was maintained for 30 minutes (Zavon and Kindel 1966).

7.2.7. Other Effects

Animal studies suggest that exposure to DDVP may be associated with immunosuppression and effects on diurnal rhythm. The effect of treating rabbits with oral doses of 0.31–2.5 mg/kg DDVP (2.5%–20% of the LD_{50}) was inhibition of both humoral and cell-mediated immune response (Desi and others 1978 and 1980). In addition, immunosuppression was observed in mice treated with 120 mg/kg DDVP (Casale and others 1983). In vitro studies on cells from embryonic renal tissue of carp demonstrated a dose-related decrease in lymphocyte proliferation and myeloid cell respiratory burst activities, both of which indicate immunosuppression. No effects on antibody production, however, were noted in in vivo studies (Dunier and others 1991).

RBC AChE activity follows a circadian oscillation in both mice and humans (Jian and Zhiying 1990). Furthermore, mortality in mice associated with exposure to DDVP is inversely related to the oscillation in AChE activity. These investigators report that DDVP interferes with the normal circadian rhythm of RBC AChE in mice and humans, noting, however, that this apparent interference may be secondary to pronounced AChE inhibition. Alterations in the diurnal rhythm of the pituitary/adrenal axis were observed in rats exposed to 2 ppm (approximately 0.3 mg/kg) DDVP in drinking water. Although effects on plasma ChE activity were not noted, levels of plasma adrenocorticotrophic hormones and adrenal cholesterol ester were altered (Civen and others 1980).

7.3. Exposure Assessment

Only two exposure scenarios are considered in this risk assessment: a child exposed to a tape strip after tampering with a trap and workers assembling traps indoors.

7.3.1. Child Tampering with a Trap

Milk carton traps contain the strip of Vaportape attached to a twist tie or simply placed in the bottom of the trap. The DDVP strip can be accessed easily and removed. Although any member of the general public could tamper with a trap, incidents such as these seem to be more plausible for children, compared with adults. In addition, using children as the exposed group is conservative because dose estimates for children, in units of mg/kg body weight, will be higher than those for adults.

Two routes of exposure may be significant, dermal contact and ingestion. For dermal exposure, the basic scenario assumes that a child removes and handles a DDVP strip. As

indicated in Table 7-3, there are reports of children as young as 2-years old being exposed to DDVP strips. This scenario is based on the assumptions that the child's age is between 2 and 3 years, that the child weighs 11 kg and has a total body surface area of 0.6 m^2 (U.S. EPA 1992).

For assessing the likelihood of systemic toxic effects, some estimate of absorbed dose is necessary. The method for making such an assessment, however, is highly uncertain. As the child manipulates the strip, some material will be transferred to the surface of the skin. Some of the chemical will be absorbed and some will volatilize. Assuming that the nature of the manipulation is such that a film of DDVP is maintained on the contaminated surface, Fick's first law may be used to estimate absorption (U.S. EPA 1992). Fick's first law requires an estimation of the K_p in cm per hour, the concentration of the chemical in a solution in contact with the skin, the area of the body surface that is contaminated, and the duration of exposure. There is no experimentally determined K_p for DDVP. Based on structure-activity relationships (equation 16), U.S. EPA (1992) estimates that the K_p for DDVP is $9.5 \cdot 10^{-4}$ cm/hour. In this scenario, the DDVP is not in solution; instead, the skin is in contact with neat or undiluted DDVP. Following the recommendations of U.S. EPA (1992), the functional concentration of DDVP is assumed to be the solubility of DDVP in water, 10 mg/mL (Worthing and Walker 1987). To apply Fick's first law, one must assume that the supply of the chemical at the exposed surface is infinite. That will not be so in this scenario because DDVP will volatilize from the surface of the skin. The most reasonable approach may be to assume that the 1 x 4 inch strip (approximately 26 cm^2) is held in a fixed position against the surface of the skin. The duration of exposure must be selected arbitrarily. For this risk assessment, a period of 1 hour will be used for the routine scenario and 4 hours will be used for the extreme scenario.

Based on the above assumptions, the routine scenario for dermal absorption would result in an absorbed dose of $2.2 \cdot 10^{-2}$ mg/kg

$$9.5 \cdot 10^{-4} \text{ cm/hour} \cdot 10 \text{ mg/cm}^3 \cdot 26 \text{ cm}^2 \cdot 1 \text{ hour} \div 11 \text{ kg} = 2.2 \cdot 10^{-2} \text{ mg/kg}.$$

For the extreme exposure, the absorbed dose would be higher by a factor of 4 ($8.8 \cdot 10^{-2}$ mg/kg). The major uncertainty in these estimates is the assumption that the functional area of exposure is 26 cm^2, the area of the strip. Assuming that rapid movement of the strip across the surface of the skin could contaminate an area of 5% of the body surface (that is, 300 cm^2) would increase the dose estimates by a factor of approximately 11. The extreme dose estimate would be approximately 1 mg/kg

$$9.5 \cdot 10^{-4} \text{ cm/hour} \cdot 10 \text{ mg/cm}^3 \cdot 300 \text{ cm}^2 \cdot 4 \text{ hours} \div 11 \text{ kg} = 1.04 \text{ mg/kg}.$$

For oral exposure, it is assumed that a child weighing between 10 and 30 kg, which corresponds to an age of 1–10 years (U.S. EPA 1989c), removes the strip of Vaportape and chews on it. In this case, the maximum dose range would be approximately 20–60 mg/kg (590 mg/30 kg to 590 mg/10 kg). This is assuming that all of the DDVP in the strip is

ingested and absorbed. Organoleptic considerations seem to make this scenario implausible, and this notion is supported by reports of poisoning episodes involving pest strips that did not result in fatalities (Gillett and others 1972a, Korninger and Lenz 1978, U.S. EPA 1981). As summarized in Table 7-4, cases in which children are exposed orally to DDVP pest strips seem to involve relatively brief periods of contact. Although these reports are somewhat sketchy, they support the position that prolonged oral exposure to a DDVP strip is unlikely.

Consequently, this risk assessment will use an oral exposure in which the child is exposed to 5% of the available DDVP as a result of oral contact with the strip. This is an arbitrary lower estimate. The actual amount will depend on the duration of exposure and the nature of the oral contact (such as chewing or swallowing). An exposure to 100% of the available DDVP in the strip will be used as the extreme scenario with the qualification that this amount of exposure may be implausible. Although these scenarios are referred to as routine and extreme, it must be emphasized that both are considered accidental. Under normal conditions, any exposure would be highly unlikely.

For carcinogenic effects, a life span average daily dose is used. This is derived by dividing the acute dose by the number of days in the reference human life span (365 days/year · 70 years = 25,550 days).

7.3.2. Workers

The milk carton traps can be assembled in two stages. The most time consuming stage is the carton assembly, in which two pre-cut perforated pieces of heavy waxed paper, similar to those used in milk cartons, are configured. In the second stage, the DDVP tape and Disparlure wick are attached to the twist tie, and the twist tie is placed in the trap. The second stage should proceed much more rapidly than the first.

During assembly, two routes of exposure may be significant, inhalation and dermal. As discussed in the program description (see section 7.1), however, both routes of exposure will be negligible if proper handling procedures are followed (that is, if the DDVP strips are installed outdoors or in a well ventilated area and dermal contact with the strip is avoided). Thus, for the routine exposure, both dermal and inhalation contact are considered negligible. For the extreme scenario, however, it is assumed that the worker does not follow proper handling procedures (that is, the trap is assembled or transported in an enclosed environment and no gloves are worn when handling the strip).

For the extreme scenario, it is assumed that an individual worker assembles 75 traps, the maximum number of traps handled per day (Table 7-1). Once the traps are fully assembled, they are placed in a garage overnight (8 hours) and are transported in a vehicle for 4 hours. The volume of the garage is assumed to be 1,500 ft^3 (10 feet · 10 feet · 15 feet) or 42.5 m^3. The volume of the driving cabin is assumed to be 160 ft^3 (8 feet · 5 feet · 4 feet) or 4.5 m^3.

There are no monitoring data regarding the levels of DDVP in air during the assembly of milk carton traps using Vaportape II. Studies are available in which DDVP was monitored in air after the placement of PVC strips impregnated with DDVP. The most relevant study was conducted by Slomka (1970). This study provides data on the levels of DDVP in air after a single Shell No-Pest strip was placed in an unventilated room and a poorly ventilated room, both of which had air volumes of 28.3 m^3. In the unventilated room, maximum levels reached approximately 0.3 mg/m^3 after about 4 days (Figure 7-1). In the poorly ventilated room, the level of DDVP in air at 4 days was approximately 0.1 mg/m^3. Over the first 24 hours, the increase in concentration in an unventilated room appears to be linear reaching approximately 0.2 mg/m^3. This corresponds to a rate of approximately 0.008 $mg/m^3 \cdot hour$ (0.2 $mg/m^3 \div 24$ hour). In a poorly ventilated room, the rate appears to be about 50% as rapid (that is, 0.004 $mg/m^3 \cdot hour$).

The data regarding the Shell No-Pest strip may not be directly applicable to this risk assessment, however, because these strips are substantially different from Vaportape II with respect to the amount of DDVP in the strip (20 g versus 0.59 g) and the dimensions of the strip (2.5 x 10 inches versus 1 x 4 inches). As discussed by Gillett and others (1972a), the rate of DDVP release from PVC is likely to depend on a number of factors including the shape of the PVC, temperature, humidity, and ventilation.

Information is available on the release of DDVP from Vaportape II. In the release study, two groups of tape samples (referred to as **A** and **B**) were weighed and assayed for DDVP at various intervals for up to 12 weeks after placement outdoors (Hercon 1994a). The results of this study, as illustrated in Figure 7-2, fit a first order model ($p < 0.00001$) with a release rate of 0.04 day^{-1}. This is close to the first order release rate of Shell No-Pest strips, 0.023 day^{-1} (Gillett and others 1972a).

These data may be used to estimate a zero-order rate for the change in concentration from a single Vaportape strip by adjusting for differences in first order release rates, the amount of DDVP in each strip, the number of strips, and the size of the room. Thus, for 75 Vaportape Strips in an unventilated garage for 8 hours, the estimated concentration is 0.16 mg/m^3

$$(0.008\ mg/m^3 \cdot hour \cdot strip) \cdot 8\ hours \cdot (0.59\ g \div 20\ g) \cdot (0.04\ day^{-1} \div 0.023\ day^{-1}) \cdot (28.3\ m^3 \div 42.5\ m^3) \cdot 75\ strips = 0.16\ mg/m^3.$$

For a poorly ventilated garage, the concentration would be about 50% of this value or 0.08 mg/m^3. For the driving scenario, the concentration in an unventilated vehicle after 4 hours would be 1 mg/m^3

$$(0.008\ mg/m^3 \cdot hour \cdot strip) \cdot 4\ hours \cdot (0.59\ g \div 20\ g) \cdot (0.04\ day^{-1} \div 0.023\ day^{-1}) \cdot (28.3\ m^3 \div 4.5\ m^3) \cdot 75\ strips = 1\ mg/m^3$$

or 0.5 mg/m^3 in a poorly ventilated vehicle. The average concentrations, assuming that the initial concentration in the vehicle was zero, would be half of these values, 0.5 mg/m^3 in an unventilated vehicle and 0.25 mg/m^3 in a poorly ventilated vehicle.

Dermal exposure will be estimated in a manner similar to that for children, using Fick's first law. For the duration of exposure, it is assumed that an individual handles 75 strips/day and that each strip requires 1 minute to install. Thus, the duration of exposure is 1.25 hours. A body weight of 70 kg is used for an adult male. Thus, the absorbed dose is $4.4 \cdot 10^{-3}$ mg/kg

$$9.5 \cdot 10^{-4} \text{ cm/hour} \cdot 10 \text{ mg/cm}^3 \cdot 26 \text{ cm}^2 \cdot 1.25 \text{ hour} \div 70 \text{ kg} = 4.4 \cdot 10^{-3} \text{ mg/kg}.$$

This exposure assessment assumes that the worker holds the strip against the skin for 1 minute. Unlike the exposure assessment for children, which may underestimate exposure, the estimated exposure for workers is likely to be an upper limit.

7.4. Dose-Response Assessment

Cholinergic toxicity is the effect of primary concern in this risk assessment. As detailed in Table 7-5, DDVP causes this effect in humans under exposure conditions similar to those described in the exposure scenarios used in this risk assessment. In addition, the significance of this effect is unequivocal. Cancer is also of concern to this risk assessment because DDVP has been classified as a potential or probable human carcinogen. All of the studies supporting the carcinogenic activity of DDVP, however, involve relatively prolonged periods of exposure. Using these studies to estimate the risks associated with short-term exposure is highly uncertain. Testicular atrophy was observed in one study after chronic exposure to 94.8 mg/kg/day (AMVAC 1989). Since this effect was observed at dose levels higher than those associated with neurological effects, a separate dose-response assessment for this effect will not be conducted.

Immunosuppression and the disruption of circadian rhythm are also associated with DDVP exposure. Effects associated with immunosuppression have been observed at exposure levels that are lower than those associated with marked AChE depression. The overall relationship of these effects to signs of cholinergic toxicity are given in Figure 7-3. Effects on immune function and circadian rhythm are not considered in the data on which the RfD is based (U.S. EPA 1994a). In three studies, immunosuppression was observed in experimental mammals exposed to DDVP. In another study, there is an indication that DDVP exposure affected the immune function in fish. The RfD and RRVs discussed below are not protective, necessarily, against these effects. The toxicological significance of the effects, however, is unclear. Several chronic studies regarding the oral toxicity of DDVP indicate that exposure to the compound did not cause adverse effects in several animal species. Nevertheless, DDVP is carcinogenic to mammals and has been associated with cancer in humans. Although DDVP may be a direct acting carcinogen (that is, DDVP is genotoxic), carcinogenicity through immune suppression cannot be ignored as a possibility or a

contributing factor. In this respect, the dose-response assessment for carcinogenicity may encompass, at least partially, concern for the effects of DDVP on immune function.

7.4.1. Cholinergic Effects

The RfD for DDVP is 0.0005 mg/kg/day (U.S. EPA 1994a) and is based on a 1-year dog feeding study in which plasma and RBC ChE inhibition was observed in males and females, and brain ChE inhibition was observed in males (AMVAC 1990). The NOAEL for this effect was 0.05 mg/kg/day and the LOAEL was 0.1 mg/kg/day. An uncertainty factor of 100 was used to derive the RfD (NOAEL ÷ 100) to reflect the uncertainties associated with interspecies extrapolation and intraspecies variability. Confidence in this RfD is ranked as medium (U.S. EPA 1994a) A confidence rating of high was not given because of dosing changes in the AMVAC (1990) study and because a rabbit developmental toxicity study and studies that fully address chronic and reproductive toxicity in rats are not available.

This RfD may not be the most appropriate index of acceptable exposure for the current risk assessment because the RfD is intended to protect against chronic oral exposures and no such exposures are anticipated in this risk assessment. The substantial amount of data on humans and other animals exposed to DDVP in a PVC matrix for relatively short periods is more directly relevant to the assessment of cholinergic effects for this risk assessment.

Data regarding the oral toxicity of DDVP in PVC matrixes are summarized in Table 7-5 and illustrated in Figure 7-3. Unlike most insecticides, for which data on human oral exposures are from accidental ingestion, the oral data on DDVP are based on clinical studies (Cervoni and others 1969, Hine and Slomka 1970, Pena-Chavarria and others 1969, Slomka and Hine 1981) conducted to support the use of DDVP as an anthelmintic (that is, a toxicant against parasitic worms). Similarly, DDVP has been used and tested as an anthelmintic in veterinary medicine (Hass and others 1971, Stanton and others 1979, Wallach and Frueh 1968).

In human clinical studies and studies on experimental mammals, inhibition of ChE activity has been demonstrated at relatively low doses. In the single-dose study by Slomka and Hine (1981), pronounced ChE inhibition was observed at relatively low doses, 0.1–6 mg/kg, administered in PVC pellets. At higher doses, up to 32 mg/kg, there is a more gradual trend toward increased enzyme inhibition. No signs of toxicity were observed in any of the exposed individuals, some of whom had ChE activity inhibited by as much as 90%. From the description of the multiple dose studies provided by Slomka and Hine (1981), some individuals in the 32 mg/kg/day dose group and some individuals in the 8 mg/kg/day dose group were developing signs of toxicity which were sufficiently severe to cause a termination of dosing before the scheduled 7 day study period. Consequently, these exposures are identified as AELs in Table 7-5.

These oral studies clearly indicate that doses of DDVP-PVC as low as 0.1 mg/kg cause plasma and RBC ChE inhibition. A NOEL for this effect has not been identified.

Nonetheless, dose levels less than 8 mg/kg have not been associated with frank effects. Studies involving repeated dose exposures to 8 mg/kg/day or less demonstrate a marked depression of plasma and RBC ChE. Although the report by Slomka and Hine (1981) is somewhat vague, it appears that some subjects either had clinically significant effects or were about to develop such effects in the judgment of the study director. Single exposures of 16 mg/kg or less, however, have not been associated with any observable effects. Only at doses greater than 100 mg/kg are clear signs of cholinergic toxicity evident (Stanton and others 1979). Furthermore, mortality was not observed in this study, even at very high doses, because the animals vomited, presumably expelling the contaminated PVC pellet.

For this risk assessment, the acute oral RRV will be set at 1 mg/kg, about a factor of 10 below the dose associated with marked AChE inhibition. This dose should not be associated with any observable effects. Exposures of approximately 10 mg/kg/day are of concern because of AChE inhibition, but frank effects are not expected to occur until exposures reach 100 mg/kg/day. This RRV can be applied to both children and adults. As discussed in the risk characterization (section 7.5.6), children (older than 1 year) do not appear to be more sensitive than adults to DDVP. This RRV will not be applied to infants, which may be a sensitive subgroup.

In addition to these oral exposures to DDVP-PVC, inhalation and dermal exposures to DDVP lead to ChE inhibition and signs of cholinergic poisoning as detailed in the various reviews cited above. These routes of exposure are of concern for workers assembling traps indoors as well as any individual touching the DDVP strip.

The TLV for DDVP is 0.9 mg/m^3 (ACGIH 1994). Based on an assessment of inhalation studies in humans, this may be associated with a 20% reduction in plasma ChE activity. Because of the carcinogenicity of DDVP, this TLV is under review. NIOSH (1981) indicate that inhalation exposures to DDVP at concentrations greater than 1 mg/m^3 require the use of a supplied-air respirator or self-contained breathing apparatus. For this risk assessment, 0.9 mg/m^3 will be adopted directly as the inhalation RRV for workers to protect against cholinergic effects. The potential carcinogenicity of DDVP is assessed as a separate risk.

The oral RRV of 1 mg/kg is not appropriate for assessing the consequences of dermal exposure because the studies on which this RRV is based used PVC-DDVP formulations. As discussed above, these formulations are less toxic than DDVP in a vehicle that allows rapid absorption. In the dermal exposure assessment, the absorbed dose of DDVP is estimated directly. Consequently, the RRV for oral exposures might be less than protective.

Zavon and Kindel (1966) provide the most directly relevant dermal exposure data from which to calculate a short-term RRV. In this study, 80.6 cm^2 sections of a DDVP strip were affixed to the skin of volunteers for 0.5 hours on 5 successive days. No significant decrease in AChE activity was observed. Using Fick's first law and assuming an average body weight of 70 kg, these exposures correspond to an absorbed dose of 0.005 mg/kg

$$9.5 \cdot 10^{-4} \text{ cm/hour} \cdot 10 \text{ mg/cm}^3 \cdot 80.6 \text{ cm}^2 \cdot 0.5 \text{ hour} \div 70 \text{ kg} = 0.005 \text{ mg/kg}.$$

This value will be divided by a factor of 10 for sensitive individuals. The resulting dermal RRV of 0.0005 mg/kg is identical to the oral RfD derived by U.S. EPA.

Assessing the consequences of exceeding the RRV for dermal exposure is difficult. As noted above, the dermal RRV should not be associated with any decrease in AChE activity; nonetheless, the RRV for inhalation exposure, 0.9 mg/m^3, may be associated with a 20% reduction in AChE activity. Assuming that all of the DDVP in inhaled air is absorbed and that an average man inhales 10 m^3 during a work day, the absorbed dose associated with the inhalation RRV is 0.13 mg/kg

$$0.9 \text{ mg/m}^3 \cdot 10 \text{ m}^3 \div 70 \text{ kg} = 0.13 \text{ mg/kg},$$

or about a factor of 25 greater than the worker RRV for dermal exposure. More severe effects, such as lethality, must be estimated from the available animal data. Gaines (1969) reported that the lowest dose lethal to female rats was 38 mg/kg for both oral and dermal exposures. Corresponding values for male rats were somewhat higher. The estimate of the LD_1 for female rats was 26 mg/kg for oral exposure and 24 mg/kg for dermal exposure. Using these data and assuming that humans are 10 times more sensitive than rats, the approximate lethal dose for humans, assuming complete absorption, is estimated at about 2 mg/kg, or a factor of about 4,000 greater than the oral or dermal RRV.

7.4.2. Cancer

The U.S. EPA classifies DDVP as a carcinogen and has conducted a quantitative cancer risk assessment on the compound. This risk assessment is based on the NTP (1989) bioassay for carcinogenicity in which pancreatic adenomas and leukemia were observed in male rats and mammary fibroadenoma and fibroma were observed in female rats. In mice, there was an increased incidence of forestomach papillomas. Based on this bioassay, a cancer potency factor for humans of 0.29 (mg/kg/day)$^{-1}$ was calculated, using the linearized multi-stage model (U.S. EPA 1994a). This value will be adopted directly for assessment of carcinogenic risk.

7.5. Risk Characterization

7.5.1. Overview

Under conditions of normal handling and use, it is unlikely that the DDVP strips will present any significant hazard to workers or the general public. If, however, the strips are not handled properly during trap assembly and transport, exposures will approach or exceed

acceptable levels. Left undisturbed, the traps pose no significant risk to members of the general public. Nonetheless, the traps may be accessible to individuals who may remove and tamper with the DDVP strip. In which case, significant and potentially hazardous exposures may occur from ingestion or dermal contact.

7.5.2. Uncertainties

The risk assessment is influenced substantially by the fact that the DDVP used in the traps is contained in a PVC matrix. This limits the rate of release and affects potential hazards for oral and inhalation exposures.

7.5.2.1. Oral Exposure

For oral exposures (that is, the consumption of the strip by a child), the available data on experimental mammals indicate that the rate of absorption into the body will be much less than that associated with the consumption of DDVP in a more readily absorbed vehicle (that is, a chemical substance used as a medium to suspend or dissolve the active ingredient). Moreover, human and animal studies indicate that ingestion of DDVP contained in a PVC matrix is less toxic than ingestion of the same amount of DDVP not contained in the matrix. In other words, the presence of PVC in the DDVP-PVC complex seems to diminish the oral toxicity of DDVP. Since data regarding oral exposure to DDVP in Vaportape II strips are not available, the question is whether to use the available human data regarding the toxicity of DDVP-PVC complexes or to use animal data regarding the toxicity of DDVP. For the risk assessment on oral exposure, the human data on DDVP-PVC complexes are used. Although this approach is not the most conservative, it is likely to result in a more realistic assessment of risk. Consequently, the RRV derived for the consumption of a strip is much greater than the RRV used to estimate the effects of dermal exposure to the strip. Data regarding the oral toxicity of Vaportape II strips would help to minimize the uncertainties in the risk assessment.

7.5.2.2. Dermal Exposure

The extent to which the PVC formulation affects the hazards associated with dermal exposure to DDVP is less clear. There are no data regarding dermal absorption of DDVP from a Vaportape II strip. Data regarding human exposure to a DDVP-PVC formulation suggest that dermal toxicity may be low; however, the study (Zavon and Kindel 1966) (see section 7.4.1) was designed in a way that it would not have detected serious effects under the conditions of exposure. There is a substantial body of human experience with DDVP contained in a PVC matrix that suggests that inadvertent or imprudent exposure to these pest strips, including dermal contact, may result in signs of intoxication; however, this experience does not support an assessment signifying the likelihood of severe effects. Nevertheless,

dermal absorption rates for DDVP estimated from empirical relationships to chemical and physical properties suggest that the amount of DDVP that could be absorbed from handling Vaportape II strips is greater than the estimated levels of acceptable exposure by factors of more than 100. Because the estimated absorption rates are based on structure-activity relationships, it may be argued that the estimates of human exposure made in this risk assessment are not realistic. These relationships, however, are well documented and validated. Moreover, it might be argued that the PVC matrix will effectively lower the absorption rate of DDVP, as is clearly the case with oral exposures; however, there are no data to support this argument.

Given the apparently high levels of dermal exposure to DDVP, the potential consequences of these exposures must be estimated. Human data regarding the oral toxicity of DDVP-PVC complexes are not appropriate for assessing dermal exposure because the PVC complex inhibits oral absorption thereby decreasing the toxicity of DDVP (see section 7.4.1.1). Animal studies are available regarding oral and dermal exposures to DDVP not contained in a PVC matrix. These studies are used in the risk assessment to estimate a dose-response relationship for humans. In extrapolating from laboratory animals to humans, the assumption is made that humans are more sensitive than laboratory animals to DDVP exposure by a factor of 10. Thus, the exposure levels from the animal studies are decreased by a factor of 10, and a human dose-response curve is derived.

The use of this uncertainty factor is arguable. The studies that permit a comparison between humans and experimental animals suggest that humans may be somewhat more sensitive, but probably not by a factor 10. On the other hand, the response of humans is generally considered more variable than that of experimental animals because of the greater genetic diversity and environmental conditions in the human population. Using animal dose-response data is likely to underestimate this diversity and consequently underestimate risk. It is not clear whether these uncertainties offset one another, and without studies designed to investigate the effects of human exposure to DDVP, the issue is not likely to be resolved.

7.5.2.3. Inhalation Exposure

Data are available regarding the release of DDVP into air from Vaportape II strips and other DDVP-PVC formulations. There are, however, no data regarding DDVP levels in air from Vaportape II strips under conditions that closely approximate those associated with the assembly or transport of the milk carton traps. Consequently, monitoring data on air levels of DDVP associated with exposure to other DDVP-PVC formulations are used, making corrections for differences in release rates and other factors that affect ambient air levels. While this introduces some uncertainties into the exposure assessment, these are minor compared with the other sources of uncertainty in this risk assessment (see sections 7.5.2.1 and 7.5.2.2).

7.5.3. Workers and the General Public

The risk characterizations for worker exposure and general public exposure to DDVP are summarized in Table 7-6. For workers involved in assembling traps and handling DDVP strips outdoors or in well-ventilated rooms, levels of the compound in air and the corresponding risks should be negligible. In poorly ventilated or unventilated rooms, however, DDVP levels as high as 0.2 mg/m^3 might be expected. Somewhat greater risks may be associated with transporting completely assembled traps (that is, traps with the DDVP strip in place). If the traps are in the passenger compartment of a vehicle, levels might reach 1 mg/m^3. This level is calculated from the estimated release rate of DDVP from 75 traps over a 4-hour period assuming little ventilation of the passenger compartment. There is a linear relationship between the number of traps in the vehicle and the duration of exposure (that is, the amount of time spent in the vehicle).

Like inhalation exposure, dermal exposure to DDVP should be negligible for workers if proper procedures are followed. If DDVP is not handled properly, the amount of absorption may vary greatly, depending on the particular activities and work habits of the individual. The exposure assessment summarized in Table 7-6 assumes that an individual handles each strip for 1 minute and that the entire surface of the strip is in contact with the skin. This is intended to represent a conservative but plausible range of exposures. Even with this conservative assessment, the projected absorbed doses of DDVP are not likely to result in toxicological effects.

Members of the public will not be at risk unless they tamper with the trap. For this risk assessment, it is assumed that a 10 kg child (approximately 3-years old) comes into contact with the trap and removes the tape. For the routine scenario involving ingestion, it is assumed that the exposure is relatively brief and that the child is exposed to only 5% of the available DDVP. For the extreme scenario, it is assumed that oral exposure is prolonged and that all of the available DDVP is consumed. The routine scenario would not be expected to result in any observable adverse effect, although AChE inhibition would be possible. In the extreme scenario, AChE inhibition is expected, and cholinergic effects might be induced. Based on the available information on poisoning incidents, both of these scenarios may be too conservative. As summarized in Table 7-4, cholinergic effects have been reported in only 1 of 17 incidents involving DDVP strips. This suggests that the bad taste of the strips will discourage prolonged and hazardous exposures.

Cholinergic effects are of substantially greater concern for dermal exposure than for oral exposure. This concern, however, is highly dependent on the exposure scenario. Using plausible exposure assumptions, relatively brief exposures to the DDVP strip may result in an absorbed dose equal to the RRV for children. In more prolonged exposures, the RRV could be exceeded by a factor greater than 100. The consequences of this exposure cannot be estimated with precision. Based on the assumption that humans are 10 times more sensitive to DDVP than are experimental mammals, the most extreme exposure summarized in Table 7-6 is still a factor of approximately 20 less than the 2 mg/kg dose at which a lethal

response is plausible. This extreme exposure is approximately equal to that associated with a decrease in AChE activity (that is, 0.1 mg/kg).

Direct dermal effects, albeit difficult to quantify, may be more likely than neurotoxic effects under normal conditions of exposure. Of the eight reports of accidental dermal exposure to DDVP in a PVC strip, four note dermal irritation or possibly an allergic reaction. As summarized in the hazard identification (see section 7.2), this is consistent with studies on experimental animals. The summaries of all of these reported incidents, however, are extremely brief, and the possibility of other agents acting as contributing factors cannot be assessed.

Cancer risks are not summarized in Table 7-6. The use of long-term bioassays to predict the consequences of extremely short-term exposures is questionable. For oral exposure, it is not appropriate to calculate cancer risks because the exposure levels, although they are expressed in units of mg/kg, do not represent absorbed doses. Instead, they are simply estimations of the exposure dose based on rough assessments of the amount of time that a child might have oral contact with a strip. For the other exposures, the highest absorbed dose is 0.09 mg/kg. When averaged over a life span, this is equivalent to a dose of 0.0000035 mg/kg/day

$$0.09 \text{ mg/kg} \div (365 \text{ days} \cdot 70 \text{ kg}) = 0.0000035 \text{ mg/kg/day}.$$

Using the cancer potency of 0.29 $(\text{mg/kg/day})^{-1}$ (U.S. EPA 1994a), the cancer risk is estimated as 0.000001 or 1 in 1 million. Given this low risk level and its attendant uncertainties as well as the certainty that cholinergic effects can be induced from short-term exposure to DDVP, there is minimal concern regarding the risk of cancer.

7.5.4. Cumulative Effects

Cumulative effects associated with DDVP exposures might be associated with repeated exposures during a single season or repeated exposures over several seasons.

For the general public, the only substantial exposures will occur from tampering with traps containing DDVP. Such incidents have not been reported despite the long use of DDVP in insect traps. These scenarios are considered in this risk assessment as accidental exposures, which occur infrequently. Consequently, it does not seem reasonable to expect that the same person will be involved repeatedly in such unusual exposures.

Workers, on the other hand, may be exposed repeatedly to DDVP if they are involved in the assembly and placement of traps over a large area, requiring several days to complete the assembly and placement. Such exposures, however, are encompassed by the RRVs used in the worker risk assessments. For inhalation exposures, the RRV is based on the TLV. As discussed in section 2, the TLV is intended to be protective of exposures that occur during a typical career (for example, 8 hours/day, 5 days/week, for 20 years). Similarly, the dermal

RRV is identical to the oral RfD, which is intended to be protective of daily exposures over a lifetime.

For some organophosphates, concern about cumulative effects is diminished because studies have demonstrated tolerance to repeated exposures (Gallo and Lawryk 1991). This tolerance has not been demonstrated for exposure to DDVP. As is true for exposures involving the general public, concern for repeated exposures is diminished because, under normal handling conditions, substantial levels of exposure are not anticipated.

As with diflubenzuron, carcinogenic risks are calculated based on the total lifetime dose. Consequently, the risks discussed above concerning 1 day of exposure will increase linearly as the duration of exposure increases. For example, if the risk of cancer associated with 1 day of exposure is 1 in 1 million, the risk associated with 5 days of exposure will be 5 in 1 million.

7.5.5. Connected Actions

There are no data regarding the effects of exposure to DDVP combined with exposure to the other agents used to control the gypsy moth or the gypsy moth itself. Inhibition of AChE is the most sensitive effect of DDVP. This effect is not associated with exposure to the other control agents or exposure to the gypsy moth. Therefore, there is no plausible basis for assuming that the effects of exposure to DDVP and any or all of the other control agents or the gypsy moth will be additive.

Exposure to other compounds that inhibit AChE are likely to lead to an additive effect with DDVP. The most common examples include any other organophosphate pesticides (Gallo and Lawryk 1991). Thus, if members of the general public or workers use other organophosphate pesticides to the extent that AChE activity is substantially inhibited, they could be at increased risk if exposed to significant levels of DDVP. As discussed in the exposure assessment (see section 7.4), however, these kinds of exposure are not anticipated.

No studies were located regarding toxicological interactions between Vaportape II and other chemicals. There are several studies regarding combined exposures to commercial grade DDVP and other chemicals, all of which involve animal exposure, and, in most cases, overtly neurotoxic doses of DDVP administered by acute injections. Of the few studies regarding oral or dermal exposure to DDVP, most involve acute durations of exposure and do not provide adequate evidence of toxicological interactions. Nevertheless, some of these studies are discussed here because they concern certain interactions that are generally associated with organophosphate insecticides as a class and because they are relevant to the issue of whether or not such interactions involving DDVP are plausible.

Phenothiazine-derived drugs such as chlorpromazine have been shown to enhance the toxicity of acutely administered organophosphate insecticides such as parathion (Calabrese 1991).

The mechanism for this enhancement is not known and may involve altered metabolic activation or deactivation of the organophosphate. The interaction between topically applied DDVP/Crotoxyphos insecticide and orally administered phenothiazine anthelmintic has been studied to a limited extent in livestock, and no obvious interactions have been observed. A series of case studies were reported in which young cattle were treated with topical doses of various organophosphate insecticides at the end of a 30-day oral treatment with phenothiazine anthelmintic, followed by DDVP/Crotoxyphos insecticide 1 month later. There was no evidence of an interaction between the phenothiazine and DDVP/Crotoxyphos insecticide (Schlinke and Palmer 1973). In a more controlled study, lambs were treated orally with phenothiazine antihelmentic (12.5 g initially and 4 days later with 6.25 g every 3 days for nine treatments) or topical application of an emulsifiable mixture of 2.3% DDVP and 10% Crotoxyphos (1,550 mL of 0.25% emulsion sprayed every 2 weeks for three applications) or both. Erythrocyte acetylcholinesterase inhibition and clinical signs of acetylcholinesterase inhibition occurred within 40 minutes after each DDVP/Crotoxyphos mixture spray; the severity of the effects was not affected by the concurrent phenothiazine treatment (Mohammad and St. Omer 1983 and 1985).

Because of their ability to inhibit acetylcholinesterase and thereby alter the metabolism and deactivation of acetylcholine, organophosphate insecticides are expected to interact with drugs that mimic the effect of acetylcholine (cholinergic drugs) or that block the effects of acetylcholine (anticholinergic drugs). In fact, the anticholinergic drug, atropine, is indicated for treatment of severe cholinergic symptoms of organophosphate insecticide toxicity. Because both cholinergic and anticholinergic drugs have many other uses, inadvertent interactions in which the organophosphate insecticide alters the effect of the drug also should be considered. Acute interactions of this type involving DDVP have been studied only to a limited extent in animal models of peripheral cholinergic control mechanisms. In one such study, the anticholinergic drug, atropine, was administered to dogs (0.022 mg/kg by intramuscular injection) 90 minutes after an acute oral dose of 60 mg/kg DDVP, and the heart rate was monitored for cholinergic (decreased rate) and anticholinergic (increased rate) effects. Although the DDVP dose alone had no effect on heart rate, it did attenuate the acceleration of the heart rate caused by atropine. The DDVP dose decreased plasma and erythrocyte cholinesterase by approximately 50% (Dellinger and others 1987). This study suggests that interactions in which DDVP affects the actions of anticholinergic drugs (for example, atropine, scopolamine, belladonna alkaloids) are plausible; however, there is no evidence of such interactions in humans.

Chemicals that inhibit carboxyesterases such as the non-organophosphate insecticide, triorthotolyl phosphate (TOTP), have been shown to enhance the toxicity of certain organophosphate insecticides. Inhibition of carboxyesterases may be a mechanism by which certain organophosphate insecticides act synergistically (Calabrese 1991). The significance of this interaction mechanism to DDVP toxicity has not been thoroughly investigated. In a study using mice, an acute intraperitoneal dose of TOTP 3 days before DDVP treatment enhanced the toxicity of an acute intraperitoneal dose of either malaoxon or paraoxon but did not alter the toxicity of an intraperitoneal dose of DDVP. Dieldrin, administered orally 4

days before sacrifice, increased liver carboxyesterase activity but had no effect on the toxicity of subsequently administered DDVP (Ehrich and Cohen 1977). This study suggests that carboxyesterase inhibitors may have a more significant effect on malaoxon and paraoxon toxicity than on DDVP toxicity.

The interaction of DDVP with other commonly occurring chemicals in the environment has not been well studied. In rats, pretreatment with acetaminophen, a common analgesic, had no effect on the acute toxicity of DDVP (Costa and Murphy 1984).

Toxicological interactions of DDVP have not been studied extensively or well enough to be of use in quantitative risk assessment. The few studies described here suggest that certain interactions typical of the organophosphate insecticides as a class (for example, anticholinergic agents) are plausible for DDVP. Nevertheless, there is no evidence that such interactions actually occur in humans. Furthermore, the studies regarding those kinds of interactions in animals have examined single exposures and have focused only on the acute anticholinesterase activity as the toxic endpoint (usually assessed by measurements of plasma or blood cholinesterase or cholinergic symptoms). There needs to be more complete interaction bioassays that examine multiple dose levels and durations, and more complete assessments of toxicity if risks related to possible interactions are to be assessed.

7.5.6. Groups at Special Risk

Children are of primary concern to this risk assessment because one of the two major exposure scenarios, imprudent handling of the DDVP impregnated tape, would most likely involve a child. The organoleptic properties (that is, the unpleasant taste and smell) of pest strips should help to decrease the amount of exposure; however, there are reported cases of child poisoning by pest strips containing DDVP, although none of the exposures have been fatal.

Very young children (that is, infants less than 6-months old) may be at special risk because they have incompletely developed AChE systems and immature livers. Several other groups may be at special risk to all cholinesterase inhibiting compounds, including DDVP. A small proportion of the population has an atypical variant of plasma cholinesterase. This condition is known to make these individuals sensitive to succinylcholine and may make them more susceptible to exposure to DDVP and other AChE inhibitors. Other groups known to have low plasma AChE levels are long-distance runners, women in early stages of pregnancy, women using birth control pills, individuals with advanced liver disease, alcoholics, individuals with poor nutritional status, and individuals with skin diseases. Asthmatics may also be at special risk because DDVP may induce or exacerbate respiratory distress (ATSDR 1993).

Table 7-1. Summary of handling procedures for milk carton traps with DDVP strips in the United States[a]

Exposure Factor	States				
	MI	NC	OH	VA	WV
DDVP strips installed only at placement site	Yes	Yes	No	Yes	Yes
Gloves provided	No[b]	Yes	Yes	Yes	Yes
Number of traps handled/day	10-30	25	75	15 (10–30)	7–10[c]
Training manual				Yes	
Potential inhalation exposure	Minimal	Minimal	Possible	Minimal	Minimal

[a]Source: Schneeberger 1994

[b]Individuals are instructed not to handle DDVP strip directly but to handle only plastic wrapper during placement.

[c]More traps may be handled if trap sites are accessible by road.

Table 7-2. Common effects of acetylcholinesterase inhibition by site[a]

System	Receptor Type	Organ	Action	Manifestation
Parasympathetic	Muscarinic	**Eye**		
		Iris muscle	Contraction	Miosis
		Ciliary muscle		Blurred vision
		Glands		
		Lacrimal	Secretion	Tearing
		Salivary		Salivation
		Respiratory		Bronchorrhea; rhinitis; pulmonary edema
		Gastrointestinal		Nausea; vomiting; diarrhea
		Sweat		Perspiration
Sympathetic (sympatholytic)		**Heart**		
		Sinus node	Slowing	Bradycardia
		Atrioventricular (AV) node	Increased refractory period	Dysrhythmia; heart block
		Smooth Muscle		
		Bronchial	Contraction	Broncho-constriction
		Gastrointestinal		Vomiting; cramps; diarrhea
		Sphincter	Relaxation	Fecal incontinence

Table 7-2. Common effects of acetylcholinesterase inhibition by site[a]

System	Receptor Type	Organ	Action	Manifestation
		Bladder		
		Fundus	Contraction	Urination
		Sphincter	Relaxation	Urinary incontinence
Neuromuscular	nicotinic	**Skeletal**	Excitation	Fasciculations; cramps followed by weakness; pupillary dilation; loss of reflexes; paralysis
		Heart	Excitation	Tachycardia
Central nervous		**Brain/Brainstem**	Excitation (early)	Headache; malaise; dizziness; confusion; manic or bizarre behavior
			Depression (late)	Depression, then loss of consciousness; respiratory depression; respiratory (diaphragm) paralysis

[a]Modified from ATSDR 1993

Table 7-3. Incidents of predominantly dermal exposure to DDVP pest strips[a]

Individual(s)	Nature of Exposure	Effect
8-year-old	Playing with a cat wearing a flea collar	Large welts on the abdomen, arms, face, and neck
21-year-old female	Contact with dog wearing a flea collar	Possible allergic reaction
Adult male	Lying on insecticide strip	Skin irritation
2-year-old boy	Unspecified dermal contact with insecticide strip	Transient skin irritation
Two children	Handled two strips	None
3-year-old	Carried around a flea collar all day	Diarrhea (effect not clearly associated with exposure)
Three children (ages 3, 6, and 7)	Played with flea collar	None
Two children	Found playing with flea collar	None

[a]Modified from U.S. EPA 1981

Table 7-4. Incidents of predominantly oral exposure to DDVP pest strips[a]

Individual(s)	Nature of Exposure	Effect
10-month-old child	Licked pest strip	None
2-year-old girl	Chewed on resin strip	None
2-year-old girl	Placed strip in mouth	None
2-year-old girl	Sucked on flea collar containing 5% DDVP for a short time	None
Three children	Sucked on flea collar	None
2.5-year-old girl	Chewed on flea collar	None
2-year-old boy	Chewed on 3-month-old insecticide strip	Mild symptoms of organophosphate poisoning
5-year-old girl	Put flea collar in her mouth	None
5-year-old child	Sucked on flea collar for 2 minutes	None
Child <5 years	Chewed on pest strip for 0.5 minutes	None
13-month-old girl	Sucked on pest strip for 10 minutes	None
15-month-old boy	Put flea collar in mouth	None
5-year-old girl	Brief oral exposure to a flea collar	None
3-year-old girl	Brief oral exposure to a flea collar	None
19-month-old boy	Brief oral exposure to a flea collar	None
1-year-old boy	Chewed on 8-month-old flea collar	None
15-month-old boy	Put flea collar in mouth and sucked on it for a few seconds	None

[a]Modified from U.S. EPA 1981

Table 7-5. Cholinergic toxicity of DDVP given orally in PVC formulations

Species/ Description (number)	Dose, Duration	Severity/ Effect	Reference
Humans/healthy volunteers (107)	0.1–16 mg/kg, single dose	NOAEL: depression of plasma and RBC ACHE.	Slomka and Hine 1981
	17–32 mg/kg, single dose	AEL: depression of plasma and RBC ACHE; slight increase in mild and transient cholinergic effects	
Humans/ healthy volunteers (16)	1, 2, 4, or 16 mg/kg/day, 7 days	NOAEL: depression of plasma and RBC ACHE.	
Humans/healthy volunteers (4)	8 mg/kg, 3 days	AEL: marked depression of plasma and RBC ACHE.	
Humans/healthy volunteers (4)	32 mg/kg/day, 2.5 days	AEL: marked depression of plasma and RBC ACHE; signs of cholinergic toxicity (not otherwise specified)	
Humans/patients with parasitic worms (24)	6 mg/kg, single dose	NOAEL: depression of plasma and RBC AChE	Pena-Chavarria and others 1969
Humans/patients with parasitic worms (84)	12 mg/kg, single dose		
Humans/patients with parasitic worms (13)	12 mg/kg, single dose	NOAEL: depression of plasma AChE; no apparent dose-related effect on RBC AChE	Cervoni and others 1969
Monkey/NA (NA)	5-80 mg/kg, 10–21 days	NOAEL: inhibition of plasma and RBC AChE	Hass and others 1971
Monkey/NA (NA)	17.6 mg/kg, on day 1; 8.8 mg/kg, on days 2 and 3	NOAEL: no signs of intoxication	Wallach and Frueh 1968

Table 7-5. Cholinergic toxicity of DDVP given orally in PVC formulations

Species/ Description (number)	Dose, Duration	Severity/ Effect	Reference
Swine/40–60 days old (8)	180 mg/kg, single dose	AEL: vomiting in 4/8 animals; no other signs of toxic effects	Stanton and others 1979
Swine/40–60 days old (1)	240 mg/kg, single dose	NOAEL: no effects reported	
Swine/40–60 days old (9)	320 mg/kg, single dose	AEL: vomiting in 3/9 pigs; these animals had no other signs of intoxication; two animals that did not vomit had tremors, salivation, and defecation	
Swine/40–60 days old (2)	1,000 mg/kg, single dose	AEL: vomiting not explicitly reported but assumed from discussion	
Swine/21 days old (8/dose group)	1 mg/kg/day, 30 days	NOAEL: slight but not statistically significant decrease in plasma and RBC AChE	
Swine/21 days old (8/dose group)	4 and 16 mg/kg/day, 30 days	NOAEL: statistically significant decrease in plasma and RBC AChE	

NA = Not available

Table 7-6. Risk characterization for DDVP in Vaportape II

Scenario	Exposure	Hazard Quotient	Consequences
Child: Accidental Ingestion			
Routine	1–3 mg/kg	1–3	Possible AChE inhibition
Extreme	20–60 mg/kg	20–60	AChE inhibition and possibly cholinergic effects
Child: Dermal Contact			
One minute exposure	0.0004 mg/kg	1	None
One hour exposure	0.02 mg/kg	40	None
Four hours exposure	0.09 mg/kg	180	AChE inhibition
Worker: Inhalation			
Proper handling	Negligible	Negligible	None
Driving	0.5–1 mg/m^3	0.6–1	AChE Inhibition
Indoor assembly	0.1–0.2 mg/m^3	0.1–0.2	None
Worker: Dermal Contact			
Strip placement:			
Routine	Negligible	Negligible	None
Extreme	0.004 mg/kg	8	None

RRV for workers:

Dermal contact	0.0005 mg/kg
Inhalation	0.9 mg/m^3

RRV for children:

Ingestion of strip	1 mg/kg
Dermal contact	0.0005 mg/kg

Cancer potency:

0.29 (mg/kg/day)$^{-1}$ (see text for discussion)

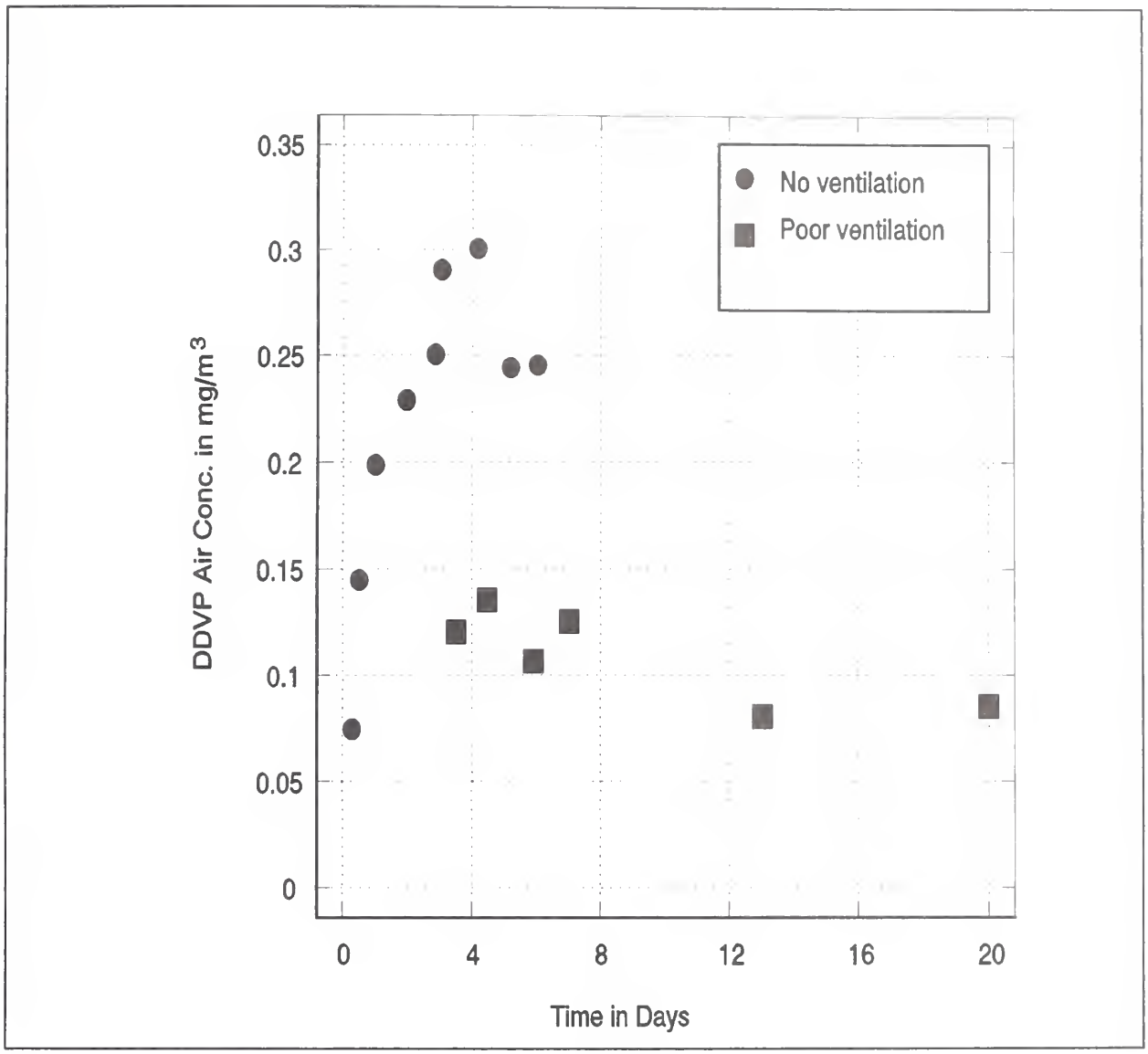


Figure 7-1. Air Levels of DDVP. DDVP air levels after the placement of a Shell No-Pest Strip in an unventilated (circles) and poorly ventilated room (squares) (Slomka 1970). In the poorly ventilated room, the level of DDVP in air at 4 days was approximately 0.1 mg/m^3. Over the first 24 hours, the increase in concentration in an unventilated room appears to be linear reaching approximately 0.2 mg/m^3.

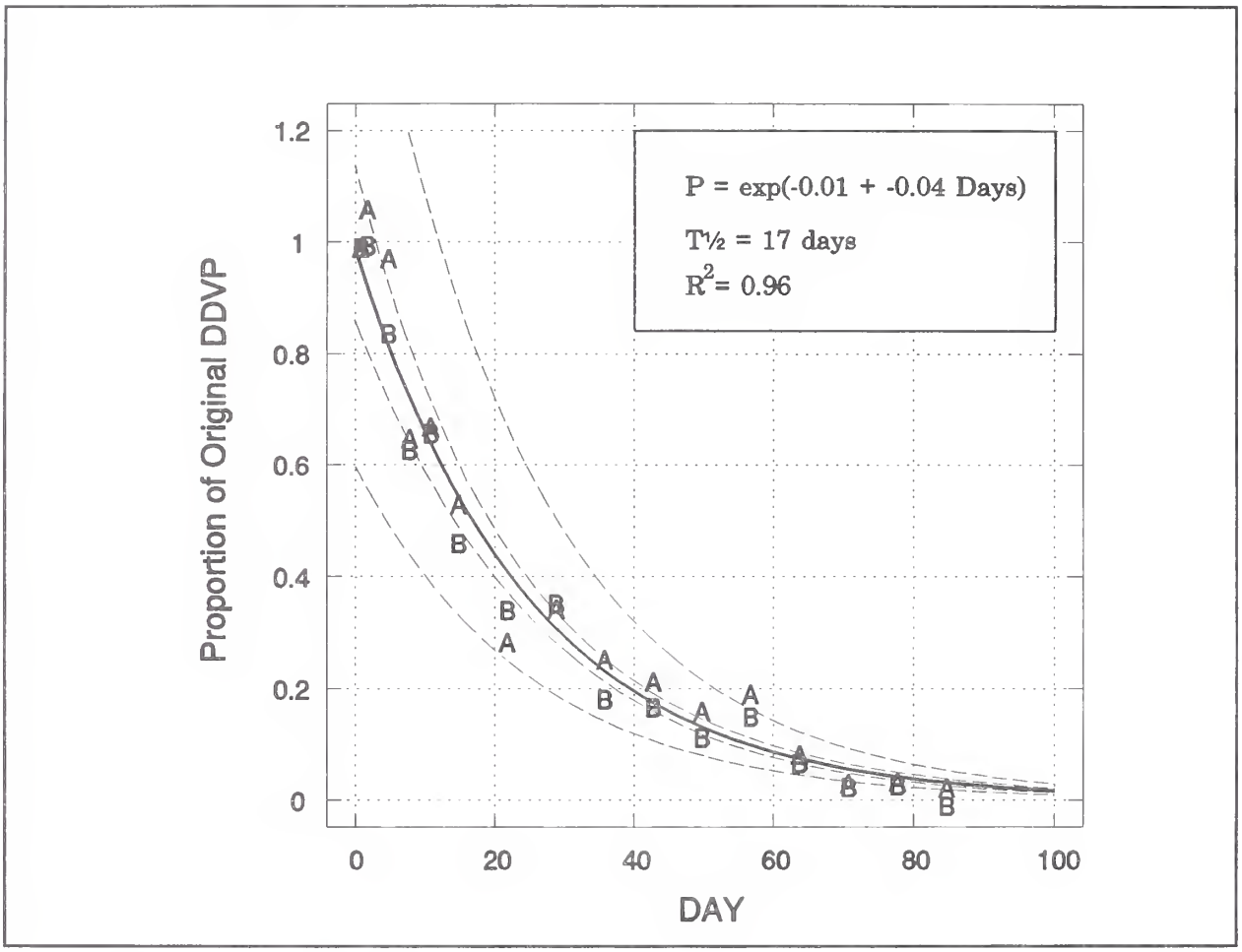


Figure 7-2. Release of DDVP from Two Vaportape II Samples, A and B (Hercon 1994).
The results of this study fit a first order model ($p < 0.00001$) with a release rate of 0.04 $days^{-1}$. This is close to the first order release rate of Shell No-Pest strips, 0.024 day^{-1} (Gillette and others 1972a).

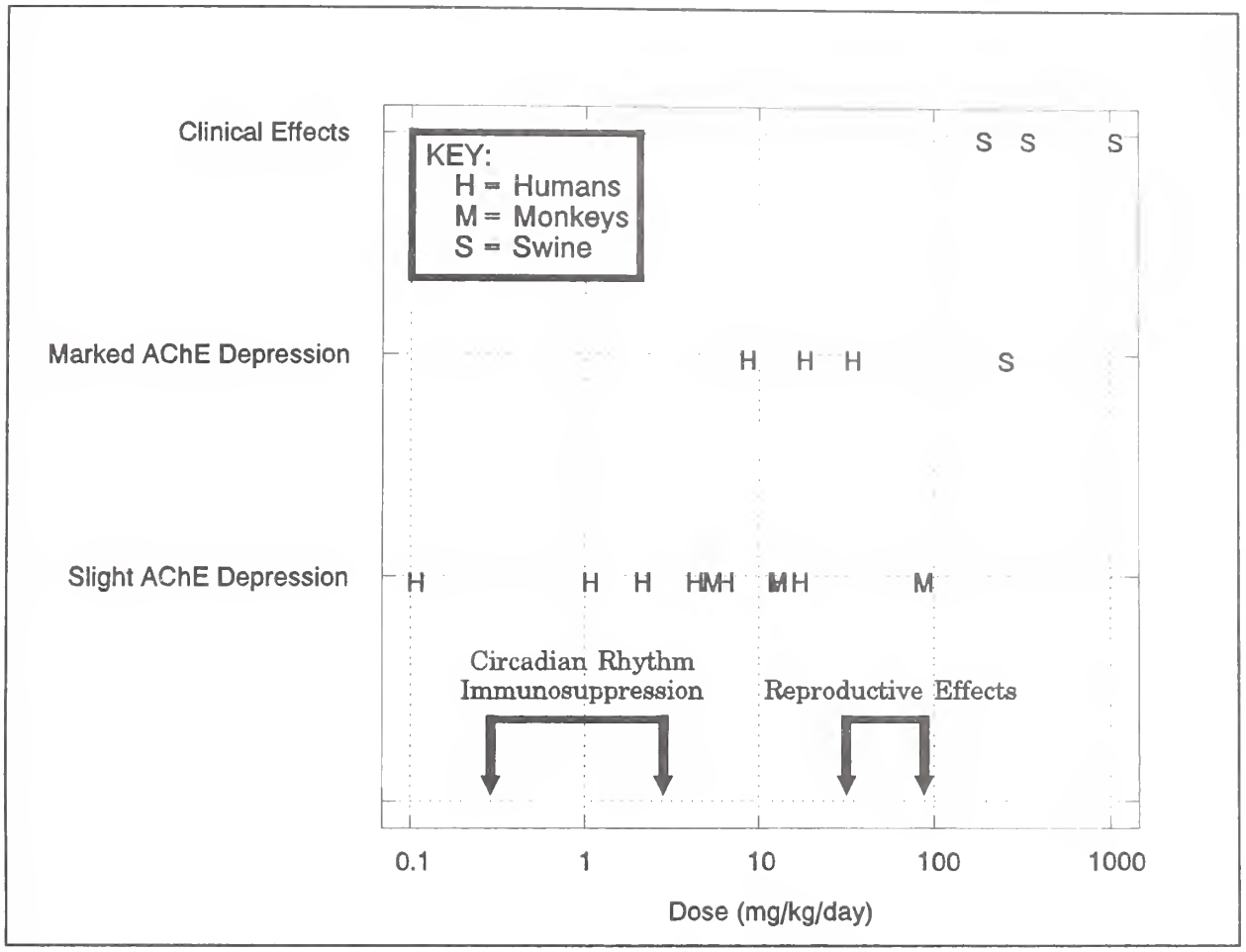
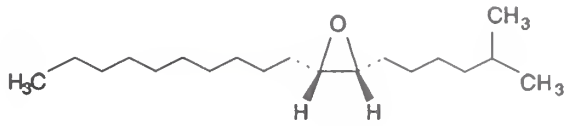


Figure 7-3. Dose-Severity Relationships for Cholinergic and Other Effects of DDVP.
Effects associated with immunosuppression have been observed at exposure levels that are lower than those associated with marked AChE depression. The RfD and RRVs may not be protective against these effects. The toxicological significance of the effects, however, is unclear. Several chronic studies regarding the oral toxicity of DDVP indicate that exposure to the compound did not cause adverse effects in several animal species.

8. Disparlure

8.1. Program Description

(+)Disparlure is a naturally occurring insect pheromone (attractant) synthesized by the female gypsy moth to attract the male gypsy moth. The molecular structure of Disparlure (cis-7,8-epoxy-2-methyloctadecane) is:



In gypsy moth programs, two forms of Disparlure are used: the (+)enantiomer and the racemic mixture, a 50:50 blend of the (+)enantiomer and (-)enantiomer. The term **enantiomer** refers to molecules that are structurally identical except for differences in the 3-dimensional configuration. For Disparlure, the (+)enantiomer is the biologically active form (that is, the form that attracts the male gypsy moth). Racemic Disparlure is used as a control agent. It is broadcast over relatively large areas and disrupts mating by confusing male moths. The product is applied by aerial spray before the emergence of gypsy moth adults, and a second application may be used later in the season.

The application rate specified on the label of Disrupt II is 10 kg product/61.6 acres. The label indicates that this is equivalent to 30.4 g ai/acre (Hercon n.d.); however, the proportion of active ingredient, 0.179, indicated on the label suggests an application rate of 29.1 g ai/acre

$$0.179 \text{ g ai/acre} \cdot 10{,}000 \text{ g} \div 61.6 \text{ acres} = 29.1 \text{ g ai/acre.}$$

The (+)enantiomer of Disparlure, also referred to as (+)Disparlure, is used as an attractant or bait in two types of traps: milk carton traps that also contain DDVP (section 7), and delta traps that do not contain an insecticide. These traps are used to monitor existing (endemic) populations and detect new infestations. Since the early 1980s, (+)Disparlure has been formulated as 3 x 25 mm plastic laminates (two outer layers of 50 μm PVC with an inner polymeric layer containing 500 μg (+)Disparlure). In fiscal year 1994 (that is, October 1, 1993 to September 30, 1994), USDA ordered 33,750 milk carton traps and 334,750 delta traps. This is equivalent to an annual use of approximately 0.18 kg Disparlure

$$0.5 \text{ mg/trap} \cdot (33{,}750 + 334{,}750) \text{ traps/year} = 184{,}250 \text{ mg} \simeq 0.18 \text{ kg}$$

or 0.4 pounds

$$0.18 \text{ kg} \cdot 2.2 \text{ pounds/kg} = 0.4 \text{ lbs.}$$

Recent evaluations have been made of a new formulation containing 500 μg (+)Disparlure on a piece of PVC twine that is 16.7 cm long (Leonhardt and others 1993) and traps baited with 1 μg (+)Disparlure (Thorpe and others 1993).

8.2. Hazard Identification

8.2.1. Commercial Formulation: Inerts and Contaminants

The only formulation of racemic Disparlure currently in use is Disrupt II. Hercon Environmental Company has registered this product with the U.S. EPA. Disrupt II contains 17.9% Disparlure and 82.1% carrier flakes. A sticker is used to hold the flakes on treated foliage or plant parts. Diatomaceous earth is added to the flakes before they are shipped to facilitate flowability (that is, to prevent the flakes from sticking together). Pertinent data regarding contaminants in the commercial formulation of Disparlure were not located in the available literature.

8.2.2. Biological Activity

Insect pheromones are relatively nontoxic to mammals (Jacobson 1977). Consequently, U.S. EPA requires less rigorous testing of these products than is required of insecticides (U.S. EPA 1994b).

Except for some standard acute studies, summarized in Tables 8-1, 8-2, and 8-3, few data are available regarding the biological activity of Disparlure. USDA funded the acute toxicity studies on Disparlure during its development for use in the gypsy moth control program. The studies were conducted by Industrial Bio-test and submitted by Hercon Environmental Company to the U.S. EPA, as part of the registration package (Hercon 1978). Summaries of these studies are published in the open literature (Beroza and others 1975).

Acute oral exposure to 10,250–34,600 mg/kg Disparlure was not lethal to Sprague-Dawley albino rats (LD_{50} greater than 34,600 mg/kg) (Beroza and others 1975, Hercon 1978). Disparlure was administered, undiluted, by gavage, and the rats were observed for 14 days after exposure. Necropsy revealed no pathological alterations in any of the treated rats. At all dose levels, however, the animals exhibited hypoactivity, ruffed fur, and diuresis. No control group was used.

The acute dermal toxicity of Disparlure was tested using four young adult New Zealand rabbits (Beroza and others 1975, Hercon 1978). When applied, undiluted, to the shaved backs of the rabbits, 2,025 mg/kg caused local skin reactions (Table 8-2) after 24 hours of contact with the epidermis. No other dose levels were tested. The rabbits were observed for 14 days after exposure, and the effects observed during this period included dryness

(escharosis), skin flaking (desquamation), hemorrhaging, and fissures after 7 days and desquamation, fissures, and pustules after 14 days. Necropsy revealed no pathological alterations other than the effects on the skin. None of the rabbits died as a result of treatment (LD_{50} greater than 2,025 mg/kg).

In a study designed to investigate the acute toxicity of inhalation exposure to Disparlure, 10 albino rats were exposed to an aerosol of the compound for 1 hour (Hercon 1978). The calculated average concentration of the aerosol was 5.0 mg/L air. The rats were observed for 14 days after exposure. None of the rats died as a result of exposure.

The same investigators tested the primary skin irritation of Disparlure using young albino New Zealand rabbits. A concentration of 0.5 mL of undiluted compound was applied to each of two test sites on each rabbit. The test sites, located lateral to the midline of the shaved back, were approximately 10 cm apart from one another, and one site was abraded while the other remained intact. The sites were occluded with gauze patches for the duration of the 24-hour exposure period, after which the intact and abraded test sites were examined. The sites were examined and scored again after 72 hours. As indicated in Table 8-2, there were signs of skin irritation.

Eye irritation was assayed in six young New Zealand rabbits exposed to 0.1 mL Disparlure (Beroza and others 1975, Hercon 1978). The compound was instilled into the right eye of each rabbit (the left eye served as a control) to determine the extent of irritation or damage to all three ocular tissues (that is, cornea, iris, and conjunctiva). The severity of ocular lesions was monitored at intervals of 24, 48, and 72 hours. Three of the six rabbits had redness of the conjunctiva at 24 hours, but no effects were observed in any of the rabbits at the later observation periods (Table 8-3). No effects were observed 7 days after exposure.

Other than the acute toxicity tests, little information is available regarding the biological effects of Disparlure. Assays have been conducted using Disparlure and several natural and xenobiotic epoxides to determine the ability of each to induce epoxide metabolizing enzymes (Moody and others 1991). Male mice were given 500 mg/kg/day Disparlure by intraperitoneal injection for 3 days. This was the maximum dose tested in preliminary range finding studies. Exposure to the compound had no effect on relative liver weight, using matched controls, or microsomal protein. Relative cytosolic protein was significantly ($p < 0.05$) increased by 18% over control values. Disparlure also caused a moderate but statistically significant ($p < 0.05$) increase in microsomal cholesterol epoxide hydrolase activity.

Disparlure appears to persist in humans for extremely long periods of time. Some humans who have come into contact with Disparlure attract the male gypsy moth for several years (Cameron 1981 and 1983).

8.3. Exposure Assessment

Inhalation exposure can be estimated from the available monitoring studies. Caro and others (1981) investigated the distribution and persistence of three Disparlure formulations including gelatin microcapsules, laminated plastic flakes, and hollow fibers. Each formulation was applied at a rate of 500 g ai/hectare (approximately 200 g/acre). In this study as well as in the other studies discussed below, a high application rate, relative to the projected rates used in program activities, was necessary in order to be able to detect Disparlure in air. Initially, air concentrations ranged from approximately 22 to 30 ng/m^3 (nanograms per meter cubed) for microcapsules and fibers and from 7.3 to 8.2 ng/m^3 for flakes. Other investigators using the same application rate reported similar initial concentrations of Disparlure in air, approximately 28-30 ng/m^3 for gelatin microcapsules and laminated plastic flakes (Taylor 1982). At a lower application rate (250 g ai/hectare), there were somewhat higher levels, 44.5-99.3 ng/m^3, using gelatin microcapsules (Plimmer and others 1978).

Over time, the concentrations in air will decrease as the Disparlure dissipates. After 30 days, air concentrations ranged from approximately 0.4 to 2.5 ng/m^3 for all formulations (Caro and others 1981). Flakes that originally contained 7.1% Disparlure (w/w) contained 6.0% (w/w) Disparlure (85% of the original level) by 30 days after treatment.

Greenhouse studies have shown that approximately 50%-80% of (+)Disparlure is released from PVC twine or laminates during a 16-week aging process (Kolodny-Hirsch and Webb 1993).

The highest reported air concentration after aerial application of 250 g ai/hectare (approximately 100 g/acre) racemic Disparlure on flakes is slightly less than 100 ng/m^3. At an application rate of 30 g ai/acre, concentrations of approximately 30 ng/m^3 can be expected. Since this estimate is based on the highest levels of Disparlure in air, actual levels of exposure could be lower.

Although the efficacy of Disparlure depends on its volatility, the studies summarized above demonstrate that 70%-85% of Disparlure may remain in the carrier matrix after prolonged periods of time. Consequently, oral exposure may occur from consumption of Disparlure flakes or tape. At an application rate of 30 g ai/acre, an individual would have to consume all of the flakes in a 1 m^2 area to receive a dose of 7.4 mg. If this were done by a 10 kg child, the dose would be 0.74 mg/kg.

Dermal exposures cannot be quantified. Based on the relationships summarized by Rubin and others (1994) and the molecular weight of Disparlure (282.5), the estimated absorption rate for this compound is approximately 2.3% day^{-1}.

8.4. Dose-Response Assessment

The toxicity data on Disparlure are not adequate for making a standard dose-response assessment. The limited available data indicate that Disparlure has a low order of acute toxicity, based on mortality as the endpoint:

Oral LD_{50} >34,600 mg/kg
Dermal LD_{50} >2,025 mg/kg
Inhalation LC_{50} >5 mg/L · 1 hour

Data regarding the toxicity of Disparlure to animals or humans after subchronic or chronic exposures were not located in the available literature. Moreover, the acute toxicity of this compound for endpoints other than mortality is poorly characterized.

Because of the limitations in the available data, no standard dose-response assessment can be made for Disparlure.

8.5. Risk Characterization

Although exposure to Disparlure is fairly well characterized, the lack of subchronic or chronic toxicity data precludes a quantitative assessment of risk. The available data regarding the acute toxicity of Disparlure indicate that the potential hazard from exposure to the compound is low, and this assessment is supported by considerations regarding structure-activity relationships and the available exposure data. Nonetheless, the lack of long-term toxicity studies adds to the uncertainty involved in characterizing risk.

8.5.1. Uncertainties

The reliance on acute toxicity data and the presumption that the toxicity of Disparlure to mammals is low because it is an insect pheromone introduces uncertainties into the risk assessment that cannot be quantified. Other uncertainties in this analysis are associated with the exposure assessment and involve environmental transport and dermal absorption. These uncertainties are relatively minor compared to the lack of subchronic or chronic toxicity data.

8.5.2. Workers and the General Public

It is not possible to develop a measure of tolerable exposure (that is, an RRV); therefore, a standard risk characterization (level of exposure divided by the RRV) cannot be developed. Nonetheless, the limited information that is available regarding the use and toxicity of Disparlure gives no clear indication of hazard. For racemic Disparlure, for example, the plausible levels of oral exposure are about 1 mg/kg. This is a factor of 10,000–35,000 less

than the exposure concentrations that were not lethal to rats. Similar ratios can be obtained for other routes of exposure. For (+)Disparlure, the ratio of plausible oral exposure to exposures that were not lethal to rats is approximately 20,000–70,000. Empirical relationships between acute exposure levels that are lethal to experimental mammals and subchronic or chronic NOAELs in experimental mammals (for example, Dourson and Stara, 1983) do not suggest that the use of Disparlure to control of the gypsy moth is likely to pose a substantial hazard to humans.

The only clear and unequivocal biological activity of Disparlure is its ability to attract the male gypsy moth. Because Disparlure is highly persistent in humans, dermal contact with the compound might make an individual an attractant to male moths for a long time. Although this is not likely to cause adverse health effects, it is likely to be a nuisance.

8.5.3. Cumulative Effects

Very little information is available on the toxicity of Disparlure. As noted above, the ability to attract the male gypsy moth is the only clear biological activity of this compound. Since this compound seems to persist in humans for prolonged periods, repeated exposures are more likely than single exposures to transfer sufficient quantities of Disparlure to the individual to attract the moth. Although this consequence of exposure to Disparlure may be a nuisance, it is not an adverse health effect.

8.5.4. Connected Actions

No information is available on the interaction of Disparlure with other control agents or other chemicals usually found in the environment. There is an obvious and substantial interaction of Disparlure with the adult male gypsy moth. Individuals who are exposed to sufficient quantities of Disparlure and who live in an area in which male gypsy moths reside will attract the moth. The definition of a sufficient quantity of Disparlure, however, cannot be characterized from the available data.

8.5.5. Groups at Special Risk.

The hazard identification for Disparlure is essentially negative. This is to say that the toxic effects of Disparlure, if any, have not been identified. Consequently, groups at special risk, if any, cannot be characterized. Because Disparlure attracts the male gypsy moth, individuals who have an aversion to insects might be considered to be a sensitive subgroup. Nonetheless, this aversion and sensitivity would not be related to any frank health effect.

Table 8-1. Acute oral toxicity of Disparlure[a]

Species/Strain	No./Sex	Dose (mg/kg)	Body Weights (g)		Effects	Mortality Dead/Tested
			Day 0	Day 14		
Rats/Sprague-Dawley	1-M	10,250	224	333	Hypoactivity ruffed fur, diuresis	0/4
	2-M		228	365		
	3-F		206	237		
	4-F		200	232		
Rats/Sprague-Dawley	5-M	15,380	230	312	Hypoactivity ruffed fur, diuresis	0/4
	6-M		230	340		
	7-F		173	220		
	8-F		169	211		
Rats/Sprague-Dawley	9-M	23,070	223	346	Hypoactivity ruffed fur, diuresis	0/4
	10-M		229	358		
	11-F		225	268		
	12-F		201	226		
Rats/Sprague-Dawley	13-M	34,600	237	360	Hypoactivity ruffed fur, diuresis	0/4
	14-M		237	354		
	15-F		222	253		
	16-F		195	237		

[a]Source: Hercon 1978

Table 8-2. Acute dermal toxicity of Disparlure[a]

Species/Strain	No./Sex	Dose (mg/kg)	Body Weights (g)		Effects
			Day 0	Day 14	
Rabbit/New Zealand	1-M	2,025	2.66	2.48	Local skin reactions after 24 hours of exposure included red, well-defined erythema and severe edema (area raised >1 mm). After 7 days of observation, escharosis, desquamation, hemorrhaging, and fissures were noted. Desquamation, fissures, and pustules were noted after 14 days.
	2-M		2.64	2.45	
	3-F		2.40	2.30	
	4-F		2.46	2.10	

[a]Source: Hercon 1978

Table 8-3. Eye irritation test for Disparlure[a]

Species/Strain	Animal No.	Concentration (mL)	Effects		
			Scoring Intervals (hours)		
			24	48	72
Rabbit/New Zealand	1	0.1	Diffuse, deep crimson red of the conjunctiva; individual vessels not easily discernible	None	None
	2		None	None	None
	3		Redness to the palpebral conjunctiva only; vessels definitely injected above normal	None	None
	4		Diffuse, deep crimson red of the conjunctiva; individual vessels not easily discernible	None	None
	5		None	None	None
	6		None	None	None

*Source: Hercon 1978

9. Comparison and Summary of Risk Assessments

9.1. Overview

Exposure to any chemical or biological agent will be associated with some level of risk, and the risk will be assessed with some level of uncertainty. To put it more generally, any human activity, including inactivity, is accompanied by risk and uncertainty. The decision to engage or not to engage in an activity is based, at least implicitly, on a comparison of risks among various options and an assessment of the benefits associated with those options.

For this risk assessment, information on each agent under review has been used to identify potential toxic effects (hazard identification), determine exposure levels associated with these effects (dose-response assessment), estimate levels to which individuals may be exposed (exposure assessment), and discuss the consequences of such exposure (risk characterization). Each phase of this assessment is accompanied by uncertainties, imposed either by limitations in the available data or limitations in the ability to extrapolate the available data to exposure scenarios of concern to this risk assessment. This risk comparison is intended to place both the numerical assessments and the uncertainties into perspective in terms of the problem--the gypsy moth--and control methods for dealing with the gypsy moth.

This assessment addresses the risks to workers and the general public of five control methods for the gypsy moth: commercial formulations of B.t.k., gypsy moth NPV, diflubenzuron, DDVP, and Disparlure. In addition, the risk assessment considers the potential adverse human health effects of exposure to the gypsy moth. This last consideration is extremely important to the risk comparison. Many insect pests cause economic or aesthetic damage. These factors are not considered in a human health risk assessment. The gypsy moth, however, also causes adverse health effects, and these effects must be considered in the assessment of any treatment strategy, including inaction.

9.2. Potential Hazards

The most relevant distinction among the compounds covered in this risk assessment relates to exposure potential. B.t.k., gypsy moth NPV, diflubenzuron, and Disparlure may be broadcast over large areas. Hence, the general public and workers involved in the field operations to control the gypsy moth are likely to be exposed to these agents. DDVP, on the other hand, is placed inside of gypsy moth traps. Under normal conditions, substantial levels of exposure are far less likely.

Three of the five control agents, B.t.k., gypsy moth NPV, and diflubenzuron, are comparable in that they are relatively specific insecticides. Disparlure, which is also very specific to the gypsy moth, does not kill the organism but disrupts mating. DDVP is a broad spectrum insecticide--it can affect the nervous system of a number of different organisms,

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Three of the five control agents, B.t.k., gypsy moth NPV, and diflubenzuron, are comparable in that they are relatively specific insecticides. Disparlure, which is also very specific to the gypsy moth, does not kill the organism but disrupts mating. DDVP is a broad spectrum insecticide--it can affect the nervous system of a number of different organisms,

including man. From the perspective of human health risk assessment, however, the distinction between the insecticides and Disparlure is not particularly relevant. That the mode of insecticidal action of B.t.k., gypsy moth NPV, and diflubenzuron on the gypsy moth is relatively specific does not necessarily mean that these compounds have no other modes of action that might affect human health. Similarly, the mode of action of Disparlure on the gypsy moth has no human health implications. Nonetheless, this does not demonstrate or even imply that Disparlure will not induce other effects in mammals.

There are differences among the kinds of risks posed by the various agents. The gypsy moth, B.t.k. formulations, and gypsy moth NPV cause the same general types of effects: skin, respiratory, or eye irritation. These effects are not life threatening or debilitating and are reversible. DDVP and perhaps diflubenzuron may pose a carcinogenic risk. For DDVP, evidence supporting a carcinogenic risk is relatively compelling. For diflubenzuron, the evidence is tenuous. Both DDVP and diflubenzuron also pose risks of reversible toxic effects. diflubenzuron affects red blood cells and DDVP affects the nervous system. At sufficiently high doses, both compounds may cause frank toxic effects that may be life threatening. At lower doses, the effects are clinically insignificant. For both diflubenzuron and DDVP, these thresholds, or nontoxic dose levels, can be relatively well defined. The potential toxic effects of Disparlure cannot be identified because very little toxicity data are available on this compound.

9.3. Uncertainties

Although uncertainties are inherent in the risk assessments for each of the agents under review, these uncertainties vary substantially, as illustrated in Table 9-1. For both the gypsy moth and B.t.k. formulations, the risk assessment can be based directly on human data, which substantially decreases the amount of uncertainty associated with species to species extrapolation. Similarly, the exposure assessments for both agents are also based on human data.

There are no data regarding health effects in humans after exposure to gypsy moth NPV, but standard toxicity studies using rodents are available. A major uncertainty with the risk assessment on gypsy moth NPV is that one effect of concern--irritant effects due to the presence of gypsy moth parts--cannot be characterized adequately in the absence of human exposure and dose-response data.

The toxicity of diflubenzuron is very well characterized in a number of laboratory species for the endpoint of primary concern--effects on hemoglobin. Although no human toxicity data are available on diflubenzuron, the relationship of the effects on hemoglobin to the development of frank toxic effects is relatively well characterized in humans. The exposure assessments for the general public require relatively few assumptions. Most scenarios are reasonably simple or are based on monitoring data on diflubenzuron. For workers, exposure must be estimated by analogy to other compounds. These estimates are associated with a

higher degree of uncertainty; however, the specific assumptions used in this risk assessment are conservative and probably overestimate risk.

For DDVP, there is a relatively substantial body of human experience in the use of DDVP in PVC strips. The greatest uncertainty in this risk assessment is associated with health effects in children after oral and dermal exposure to DDVP, from tampering with a trap. If applied directly to the skin, DDVP is likely to be well absorbed. In gypsy moth control programs, however, the DDVP is contained within a plastic slow-release strip. This reduces the rate of absorption of DDVP after oral exposure. This is well documented and directly affects the risk assessment for oral exposure. For dermal exposure, however, the effect of the plastic strip on the rate of absorption is not well documented. Consequently, a conservative approach is used to assess the risk of direct dermal contact with the DDVP strip. For oral exposure, the amount of DDVP in each pest strip is sufficient to cause extremely serious and perhaps lethal effects if administered, to a young child, as a single dose of liquid DDVP. The containment of DDVP in the PVC matrix, however, will decrease the rate of absorption. In addition, the available data on human poisonings suggest that prolonged oral exposure is unlikely, possibly because of the objectionable taste of the pest-strip.

The databases are incomplete for all of these agents. There is the possibility that any or all of these agents may be associated with effects that have not been identified by the available toxicity or epidemiology studies. Although these are legitimate concerns, they are equally applicable to all agents as well as the gypsy moth and are, therefore, of limited use in any comparisons of risks or the uncertainties associated with those risks.

9.4. Estimated Risks

The quantitative risk characterizations for the gypsy moth and each of the control agents are summarized in Tables 9-2 and 9-3. Table 9-2 summarizes risks for routine exposures. Table 9-3 summarizes risks for extreme exposure. The routine and extreme scenarios for the general public are also summarized in Figure 9-1.

In most cases, risk is expressed in two forms: the hazard quotient (HQ) and extra risk. As discussed in section 2, the HQ is simply the anticipated level of exposure divided by some measure of acceptable exposure. HQs that are less than or equal to unity (that is, the anticipated level of exposure is less than or equal to the level of acceptable exposure) indicate that adverse effects are not expected to occur as a result of exposure. Although the use of HQs is a common approach in risk assessment, HQs are of limited usefulness when the level of exposure exceeds the RRV (that is when the HQ is greater than 1). Because of the conservative methods used to derive levels of acceptable exposure as well as the uncertainties associated with both exposure assessments and dose-response assessments, HQs greater than 1 do not clearly suggest the nature or even the likelihood of observing adverse effects.

Because of these limitations in the HQ, quantitative response estimates are made, whenever possible, and the nature of the likely effect is indicated (Tables 9-2 and 9-3). Details of these summaries are included in the appropriate sections for each agent. The nature of the dose-response model used for these estimates is agent or effect specific. For instance, all cancer risks are upper limits of risk based on a mathematical model, as discussed in the risk assessments methods (see section 2). For the gypsy moth, risks are based on a log-exposure probit-response model (see section 2.5). For other compounds, no formal model is used, and the estimates of risk are only semi-quantitative.

For routine exposure (Table 9-2), the central or most plausible estimates of exposure are used. For the gypsy moth itself, moderate and heavy infestations are assumed. For extreme exposure (Table 9-3), the nature of the exposure depends on the agent. For diflubenzuron and DDVP, exposure assessments for the general public are based on plausible accidental exposures, as discussed in the individual risk assessments. For the gypsy moth and B.t.k. formulations, the most conservative exposure scenarios and dose-response estimates are used. Although these scenarios may not be quite as extreme as the accidental scenarios, they are relatively comparable to the accidental scenarios.

9.5. Qualitative Assessments

Given the uncertainties in the quantitative assessments, the primary use of these values in a comparative risk assessment is to make a qualitative determination about which actions--treatment or no treatment--pose the least risk. These qualitative assessments are summarized in Table 9-4 and discussed in the following paragraphs.

9.5.1. The Gypsy Moth

The clearest and least equivocal indications of risks are associated with exposure to the gypsy moth itself. During a major infestation, a significant proportion of the population will experience skin irritation. The available epidemiology studies indicate that a substantial proportion of affected individuals will seek medical attention. Although the potential for respiratory irritation cannot be quantified, this effect is plausible.

9.5.2. B.t.k.

For B.t.k., there is no indication that the general public will experience any detectable adverse effects. The epidemiology data are adequate to support this assertion. Some irritant effects are plausible but the prevalence of these effects is expected to be low. Ground workers are likely to be affected in substantial numbers. The nature of these effects--irritation to the respiratory tract, skin, and eyes--are similar to but less severe than those effects caused by exposure to the gypsy moth. This assessment regarding the severity of

effects is based on epidemiology studies in which there was no detectable increase in the number of individuals seeking medical attention for effects that could be attributed to B.t.k. applications.

9.5.3. Nucleopolyhedrosis Virus (NPV)

The database for gypsy moth NPV is far less complete than that for the other biological agents. Gypsy moth NPV has not been widely used, and no epidemiology data are available. Nonetheless, the toxicity data on experimental animals suggest that the potential for effects such as eye, skin, and respiratory irritation in the general public is very low. Risks, if any, to workers cannot be assessed.

9.5.4. Diflubenzuron

Under routine exposure assumptions, diflubenzuron presents no substantial risks to workers or the general public. As detailed in the diflubenzuron risk assessment, the carcinogenic risks of diflubenzuron and 4-chloroaniline, a metabolite of diflubenzuron, are considered and summarized in Tables 9-2 and 9-3. The evidence for the carcinogenicity of 4-chloroaniline is limited. For diflubenzuron, the evidence is largely conjectural. These risks are included to demonstrate that even with highly conservative assumptions, the cancer risks associated with the use of diflubenzuron are slight. In the extreme exposure scenarios, HQs for the general public exceed unity, suggesting some level of concern. Based on an assessment of the dose-response relationships for diflubenzuron, these extreme exposure scenarios might be associated with detectable, albeit transient, changes in the blood. No overt signs of toxicity or residual damage would be expected.

9.5.5. DDVP

Under conditions of normal use and handling, DDVP presents no significant toxic or carcinogenic risks to workers or the general public. Nonetheless, DDVP is a neurotoxin. If not handled properly, mild and reversible neurological effects might be evident in workers. If members of the public tamper with a trap, similar and possibly more severe effects are likely if the exposure is prolonged. As indicated above and discussed in the DDVP risk assessment (see section 7), this conclusion is associated with a high degree of uncertainty because of the assumptions used to estimate absorbed doses. This uncertainty is reflected in Table 9-3 with HQs ranging from 1 to 60 for the general public. At the lower end of this range, it is unlikely that any effects would be detectable or clinically significant. At the higher end of the range, cholinergic effects may be observed. Although these effects might be severe, lethal exposures do not seem plausible but cannot be ruled out.

9.5.6. Disparlure

The potential effects of Disparlure cannot be assessed directly, except to indicate that plausible levels of exposure are far below levels that did not cause overt signs of toxicity in experimental mammals. By analogy to other insect attractants, the risks associated with exposure to Disparlure are likely to be very low.

9.6. Cumulative Effects

Both workers and the general public may be subject to cumulative effects through the repeated application of a control agent during a single season or the application of a control agent over several seasons. Similarly, cumulative effects from the exposure to the gypsy moth may occur by repeated contact during a single season or multiple seasons. Quantitatively, most risk assessments of the individual agents consider cumulative effects by basing the risk assessment on studies that approximate multiple exposures during a single season (such as the gypsy moth or B.t.k.) or by basing the risk characterization on levels of acceptable exposure (RRVs) that are intended to be protective of multiple exposures (such as diflubenzuron or DDVP). For gypsy moth NPV and Disparlure, standard quantitative assessments are not possible, and the potential impact of cumulative effects cannot be quantitatively addressed.

The impact of cumulative effects over several seasons is more difficult to characterize. For the biological agents, responses associated with allergenic reactions are possible. For the gypsy moth, some data suggest an allergic component in the responses of some individuals. For the other biologicals, allergic components are plausible. Thus, for some sensitive individuals, cumulative effects that cannot be addressed directly in the quantitative assessment are possible. Except in the case of the gypsy moth, however, the probability of these effects occurring in response to program related activities is based on conjecture.

For the chemical agents, the potential significance of cumulative effects associated with exposure over several seasons varies with the endpoint. The most sensitive toxic effect for DDVP is acetylcholinesterase inhibition. For diflubenzuron, the most sensitive effect is methemoglobinemia. For both of these effects, a plausible basis for cumulative effects associated with intermittent exposure over several seasons is not apparent. Both of these compounds, however, are also associated with potential carcinogenic risks. Although these risks are very low, repeated exposure over several seasons could result in a cumulative increase in risks. For example, if the estimated risk is 1 in 1 million for exposures occurring over a single season, exposure for two seasons would result in risk estimates of 2 in 1 million.

9.7. Connected Actions

In general, there is no reason to expect that exposure to more than one agent considered in this risk assessment will increase risk. For most agents, the effects appear to be quite different from one another and induced by different mechanisms. An exception may involve exposures to the gypsy moth and gypsy moth NPV. Because formulations of gypsy moth NPV contain gypsy moth parts, it is plausible that combined exposure to the gypsy moth and gypsy moth NPV may increase the risk of irritant effects characteristic of gypsy moth exposure. There are no human data regarding the toxicity of gypsy moth NPV. Consequently, this assessment of the consequences of connected actions is speculative.

The only unequivocal effect of connected actions involving the agents under review is combined exposures to Disparlure and the gypsy moth. If an individual is exposed to a sufficient quantity of Disparlure, the individual will attract the male gypsy moth. This has no direct health implications but would be a nuisance.

Both workers and the general public will, of course, be exposed to a number of other chemical and biological agents during gypsy moth infestations and during applications of gypsy moth control measures. There is a potential for toxicological interactions between the agents under review and other agents in the environment; for the most part, the nature and effects of such interactions are speculative. For DDVP, which inhibits acetylcholinesterase, exposure to other compounds that inhibit acetylcholinesterase could result in increased risk. Similarly, for diflubenzuron, exposure to other agents that induce methemoglobinemia may increase risk. No generalizations can be made about the likelihood that such exposures would be toxicologically significant, except that the likelihood would depend on the level of exposure to the specific compounds.

9.8. Groups at Special Risk

For each control agent, attempts have been made to identify groups at special risk because of disease states or some other biological variation. For the biological agents, individuals who have a history of allergies may be at some increased risk. Infants may be more sensitive than adults to the effects of exposure to DDVP or diflubenzuron. Moreover, some individuals may be less able to tolerate exposure to these compounds because of a diminished ability to recover from the effects induced by these chemicals. Although these are reasonable concerns, there is no indication that routine exposures will present a remarkable hazard to any of these individuals.

Individuals with multiple chemical sensitivity (MCS) may be extremely sensitive to even very low levels of exposure to a variety of agents. For the current risk assessment, neither the qualitative nor the quantitative significance of MCS can be assessed. The number of individuals in the population with MCS is not known. This is partly because a single set of criteria for diagnosing MCS has not been adopted. That individuals with MCS might be

responsive to the gypsy moth or one or more of the agents used to control the gypsy moth is plausible but cannot be characterized further from the available data. Although these concerns are important, they are equally applicable to all agents as well as the gypsy moth and are, therefore, of limited use in any comparison of risks.

9.9. Relative Severity of Effects

In terms of USDA actions, the clearest public health risks are associated with no treatment. In other words, the likelihood and severity of the health effects of the gypsy moth, under normal conditions of exposure, are generally greater than those associated with any of the control measures. This is not to suggest that exposure to the gypsy moth is an imminent hazard or an extreme public health concern. The health effects observed in humans after exposure to the gypsy moth appear to be transient and relatively mild. Nonetheless, affected individuals are likely to seek medical care.

The effects of the control agents, however, are for the most part equally mild. Neither B.t.k., nor gypsy moth NPV, nor Disparlure can be associated with any toxic effects requiring acute medical care. Even highly exposed individuals would probably not seek any medical care. Both DDVP and diflubenzuron, on the other hand, can be associated with effects that are life threatening. At the levels of exposure anticipated during normal use, however, no serious toxic effects are anticipated.

Table 9-1. Quality of the data supporting the risk assessments

Element	Gypsy Moth	B.t.k.	NPV	DFB	DDVP	Disparlure
Hazard identification	●	●	○	●	●	□
Dose-response assessment	●	○	◘	○	○	◘
Exposure assessment						
Workers, routine	○	●	◘	○	●	□
Workers, extreme					○	
Public, routine	●	□	□	●	●	○
Public, extreme					□	
Risk characterization						
Workers, routine	●	●	◘	○	●	◘
Workers, extreme					○	
Public, routine	●	○	◘	●	●	◘
Public, extreme					□	

Key:

● = Good: based on adequate human data.

○ = Moderate: based on animal data, analogous compound, or extrapolation.

□ = Marginal: based on tenuous extrapolation or association.

◘ = Inadequate: quantitative assessment not supported.

Table 9-2. Comparison of risks associated with routine exposure to the gypsy moth and its control agents

Agent	Public		Worker	
	HQ	Extra Risk	HQ	Extra Risk
Gypsy moth, Moderate infestation	2–17	0.2%–1% Irritation	NA	25% (10%–100%) Irritation
Heavy infestation	17–170	1%–7% Irritation	NA	25% (10%–100%) Irritation
B.t.k	1	Probably low irritation	50 [GW] 3-150	50%–100% Irritation
NPV	0.006	Probably low irritation		
Diflubenzuron	0.02	No effect on methemoglobin levels <1 in 1 million, cancer	0.005 [GW] 0.001 [AW]	No effect on methemoglobin levels <1 in 1 million, cancer
DDVP	Negligible			
Disparlure	Probably very low			

GW = Ground workers; AW = aerial workers; NA = not applicable

HQ = Hazard Quotient: Anticipated Exposure ÷ Level of Acceptable Exposure

Table 9-3. Comparison of risks associated with extreme exposure to the gypsy moth and its control agents

Agent	Public		Worker	
	HQ	Extra Risk	HQ	Extra Risk
Gypsy moth	7,000	13% (10%–50%) Irritation	NA	50% (10%–100%)
B.t.k.	2	Irritation probably low	150–360 [GW]	100% [GW]
NPV	>0.006	Probably low	Cannot assess	
Diflubenzuron	7	Detectable increase in methemoglobin levels <1 in 1 million, cancer	0.25 [GW] 0.02 [AW]	No effect on methemoglobin levels <1 in 1 million, cancer
DDVP	1–60	AChE depression, possible cholinergic effects	0.2–1	<1 in 1 million, cancer
Disparlure	Probably low			

GW = Ground workers; AW = aerial workers; NA = not applicable

HQ = Hazard Quotient: Anticipated Exposure ÷ Level of Acceptable Exposure

Table 9-4. Qualitative comparison of risk assessments

Gypsy Moth	
Public	In moderate or severe infestations, rashes or other adverse skin reactions will be prevalent, especially in children or other individuals who spend a substantial amount of time outside.
Workers	Although quantitative exposure assessments are not possible, the prevalence of individuals in the general population who are sensitive to the gypsy moth is sufficiently high to indicate that substantial numbers of workers exposed to the larvae will have irritation of the skin, eyes, or respiratory tract.
B.t.k.	
Public	If exposed to the direct spray, some individuals are likely to have minor irritation of the skin, eyes, or respiratory tract. Pathogenic effects are not likely, even in immunocompromised individuals. Allergic responses, while conceivable, have not been documented.
Workers	Ground workers will evidence transient irritation of the eyes, skin, and respiratory tract unless effective methods are developed to reduce exposures. Aerial workers may develop such effects during prolonged periods of spraying.
Gypsy Moth NPV	
Public	Irritation of the eyes, skin, and respiratory tract are possible but the likelihood of such effects cannot be assessed because of limitations in the available toxicity and exposure data.
Workers	Irritation of the eyes, skin, and respiratory tract are more likely in workers than in the general public because exposure will be higher. As with the general public, the likelihood of such effects cannot be assessed.
Diflubenzuron	
Public and Workers	No clinically significant effects are likely under either routine or extreme exposure assumptions. At high exposures, increases in certain blood pigments might be detectable. Highly conservative estimates of cancer risks are negligible, less than 1 in 1 million.
DDVP	
Public and Workers	Under normal conditions, exposure and consequent risk will be negligible. In cases of tampering with or improperly assembling a trap, AChE inhibition is likely and signs of cholinergic toxicity are possible. Severe toxic effects are unlikely but cannot be ruled out. For short-term high-dose exposures, carcinogenic risks, while conceivable, cannot be well quantified.
Disparlure	
Public and Workers	Data are not sufficient for a quantitative risk assessment. By analogy to other insect pheromones, risks of toxic effects, if any, are likely to be slight. Disparlure is very persistent in humans. Individuals exposed to Disparlure may attract adult male moths for prolonged periods of time (that is, years). This may be a considerable nuisance. The level of exposure required to cause the attractant effect cannot be characterized, although the likelihood of this effect would seem greater for workers than for the general public.

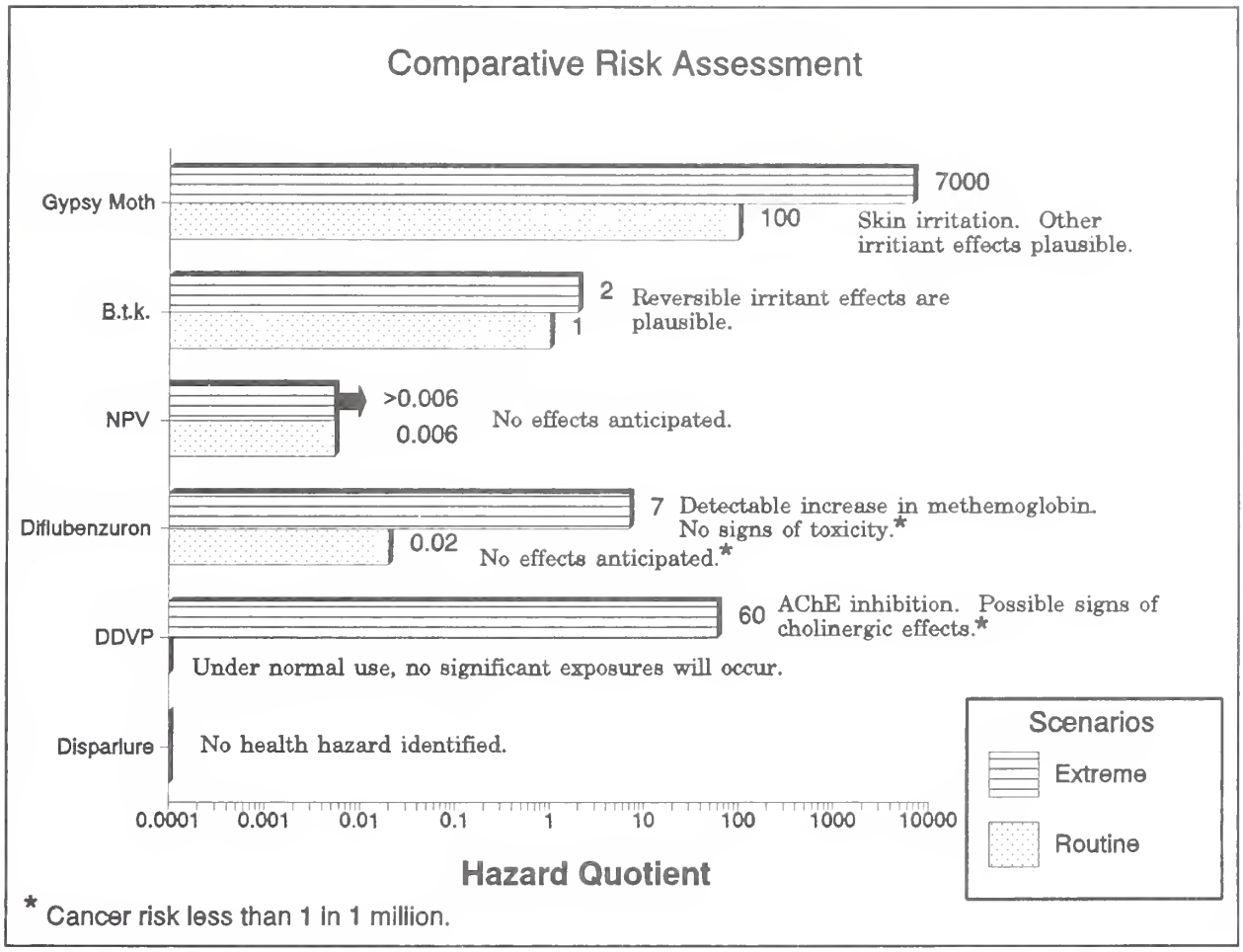

Figure 9-1. Risk Comparison for the General Public. Under routine conditions of exposure, the only agent likely to cause a substantial number of adverse health effects in humans is the gypsy moth. Under extreme conditions, the use of B.t.k. may be associated with irritant effects in some members of the general public. Dimilin might be associated with a detectable increase in methemoglobin; however, this response to exposure would not be associated with any frank toxic effect. If a trap containing DDVP is grossly mishandled, signs of toxicity (Table 7-2) may develop. The occurrence of severe toxic effects in humans after exposure to DDVP is unlikely but cannot be ruled out.

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GLOSSARY

1-Day Health Advisory -- A drinking water concentration (mg/L) not likely to cause adverse effects in the general population, including sensitive subgroups, after 1 day of exposure.

10-Day Health Advisory -- A drinking water concentration (mg/L) not likely to cause adverse effects in the general population, including sensitive subgroups, over a 10-day exposure period.

Absorption -- The process by which the agent is able to pass through the body membranes and enter the bloodstream. The main routes by which toxic agents are absorbed are the gastrointestinal tract, lungs, and skin.

Acetylcholine -- A naturally occurring chemical responsible for the transmission of impulses between nerve cells or between nerve cells and an effector cell (such as a muscle cell). Broken down to inactive compounds by acetylcholinesterase.

Acetylcholinesterase -- An enzyme responsible for the degradation of acetylcholine to acetic acid and choline. The inhibition of this enzyme leads to an excess of acetylcholine in nerve tissue. This can lead to a broad spectrum of clinical effects (Table 7-2).

Acinar-cell adenomas -- A type of benign tumor.

Acute exposure -- A single exposure or multiple exposure occurring within a short time (24 hours or less).

Adenoma -- A benign epithelial tumor.

Additive Effect -- A situation in which the combined effects of two chemicals is equal to the sum of the effect of each chemical given alone. The effect most commonly observed when two chemicals are given together is an additive effect.

Adjuvant(s) -- Formulation factors used to enhance the pharmacologic or toxic agent effect of the active ingredient.

Adsorption -- The tendency of one chemical to adhere to another material.

Adverse-Effect Level (AEL) -- Signs of toxicity that must be detected by invasive methods, external monitoring devices, or prolonged systematic observations. Symptoms that are not accompanied by grossly observable signs of toxicity. In contrast to Frank-effect level.

Aerobes -- Organisms that require oxygen.

Aesthetic Damage -- An undesirable change in appearance.

Alkaline -- Having a high pH; a basic solution, compared with an acidic solution.

Allergic Reaction -- The situation where a preexposure of the chemical is required to produce the toxic effect via an antibody.

Alopecia -- Hair loss.

Amino Acids -- Relatively simple carbon-nitrogen molecules that are the subunits of proteins.

Analogy to Other Compounds -- Using data on one set of compounds to predict the activity of another set of compounds.

Anemia -- A decrease in the concentration of red blood cells in whole blood.

Anaerobes -- Organisms that do not require oxygen.

Anthelmintic -- A compound used to rid an organism of parasitic worms.

Antibodies -- Large protein molecules that interact with antigens and deactivate antigens.

Antigen -- A substance that is capable of inducing an immune response.

Aplastic -- Pertaining to or characterized by aplasia--the lack of development of an organ or tissue, or of the cellular products from an organ or tissue.

Aplastic Anemia -- A form of anemia that is difficult to treat.

Assay -- A kind of test (noun); to test (verb).

Atrophy -- A decrease in the size of a cell, tissue or organ often associated with exposure to a toxic agent or to the lack of use of the affected organ.

Bacillus thuringiensis (B.t.) -- A bacterium, found in most of the world, that is useful for regulating or controlling insect populations. This microorganism produces several agents (toxins) that are active against insects.

Bacillus thuringiensis var. kurstaki (B.t.k.) -- A subspecies of B.t. adopted for commercial production because of its high activity against various forest-defoliating pests, including the gypsy moth.

Benign -- Not malignant, not recurrent, favorable for recovery.

beta-Exotoxin -- A proteinaceous toxin in some forms of B.t. which is mutagenic in mammals. This toxin is not present in B.t.k.

Biliary -- Referring to the bile, a substance in which many chemicals are eliminated from the body.

Biologically Sensitive -- A term used to identify a group of individuals who, because of their developmental stage or some other biological condition, are more susceptible than the general population to a chemical or biological agent in the environment.

Cancer Potency Parameter -- A model-dependent measure of cancer potency $(mg/kg\text{-}day)^{-1}$ over lifetime exposure. [Often expressed as a q_1^* which is the upper 95% confidence limit of the first dose coefficient (q_1) from the multistage model.]

Canopy -- The amount and nature of the overhead covering of vegetation.

Carcinogen -- A chemical capable of inducing cancer.

Carcinoma -- A malignant tumor.

Carrier -- In commercial formulations of insecticides or control agents, a substance added to the formulation to make it easier to handle or apply.

Caterpillar -- The larva of any butterfly and of most moths, having legs and prolegs for crawling.

Cell Mediated Response -- A response originating from materials within the cell, in contrast to a humoral response.

Chitin -- A polymer of a glucose-based molecule that comprises a substantial proportion of the outer-shell of insects.

Cholinergic -- Refers to nerve cells that release acetylcholine.

Chromatography -- A method of separating chemicals prior to quantitative analysis.

Chronic Exposure -- Long-term exposure studies often used to determine the carcinogenic potential of chemicals. These studies are usually performed in rats, mice, or dogs and extend over the average lifetime of the species (for a rat, exposure is 2 years).

Circadian Rhythms -- An influence of the time of day on the rate of metabolism of foreign compounds, often observed in a given animals species. This variation in the metabolic rate is often correlated with variations in endocrine functions as influenced by the light-dark cycle to which the animal is exposed.

Coliform -- Bacteria which when it occurs in water is usually considered evidence of fecal contamination.

Colony Forming Units(s) (cfu) -- A commonly used measure of human exposure to B.t.k. The number of cfu from aerial spray or ground spray of commercial formulations of B.t.k. is determined from viable spores contained in droplets of particulate deposited on sprayed surfaces. The droplets are collected and cultured, and the visible massess of growing bacteria (referred to as colonies) identified as B.t.k. are counted. Hence, each cfu can be formed from a droplet or particulate that contains one or more viable spores.

Common Logarithm -- The common logarithm of a number, **X**, is defined as the number, **Y**, which when used as the exponent of 10 results in **X**. Thus if $X = 10^Y$, then the log of **X** is **Y**, which is often written using the notation, $\log(X) = Y$.

Confounders -- A term used in discussions of studies regarding human populations (epidemiology studies) to refer to additional risk factors that if unaccounted for in a study, may lead to erroneous conclusions.

Congenital -- Refers to conditions that are present at birth, regardless of their causation.

Connected Actions -- Exposure to other chemical and biological agents in addition to exposure to the control agent during program activities to control the gypsy moth.

Conjugation -- In metabolism, a linkage of one molecule with another. A common step in the elimination of many chemicals from the body.

Conjunctiva -- The thin membrane that covers the eyelids and eyeball.

Conjunctivitis -- An inflammation of the membrane that lines the eyelids.

Contaminants -- For chemicals, impurities present in a commercial grade chemical. For biological agents, other agents that may be present in a commercial product.

Controls -- In toxicology or epidemiology studies, a population that is not exposed to the potentially toxic agent under study.

Corneal Opacity -- A cloudy area on the cornea.

Corneal Ulcer -- A small area of damaged tissue on the surface of the eye.

Corticosteroid -- An anti-inflammatory agent.

Corrosive Effect -- An effect that causes visible destruction and alteration in the tissue at the site of contact.

Cumulative Exposures -- Exposures that may last for several days to several months or exposures resulting from program activities that are repeated more than once during a year or for several consecutive years.

Cytosolic -- Found in the cytoplasm of a cell.

Dams -- Females.

Degraded -- Broken down or destroyed.

Degrees of Freedom -- The number of data points minus the number of parameters in a model. For example, two points are required to define a straight line. In statistical jargon, using two points to define a straight line is fitting a two-parameter model with zero degrees of freedom.

Delta-endotoxin -- A proteinaceous toxin in B.t.k. that is toxic to the gypsy moth.

Dermal -- Pertaining to the skin.

Dermatitis -- Inflammation of the skin characterized by redness, swelling, pain, and warmth.

Dislodgeable Residues -- The residue of a chemical or biological agent on foliage as a result of aerial or ground spray applications, which can be removed readily from the foliage by washing, rubbing or having some other form of direct contact with the treated vegetation.

DiPel -- One of the commercial formulations of **B.t.k.** See Table 4-1.

Diuresis -- Increased urinary excretion.

Diurnal Rhythm -- Normal changes in the body that occur cyclically during the day. Most diurnal variations have been shown to be related to the eating and sleeping habits of the test species.

Dose-response Assessment -- A description of the relationship between the dose of a chemical and the incidence of occurrence or intensity of an effect. In general, this relationship is plotted by statistical methods. Separate plots are made for experimental data obtained on different species or strains within a species.

Eczema -- A form of dermatitis associated with swelling and redness of the skin.

Effector Cell -- A cell stimulated by a nerve cell to effect a certain function. Examples include muscle and sensory cells.

Empirical -- Refers to an observed, but not necessarily fully understood, relationship in contrast to a hypothesized or theoretical relationship.

Enantiomer -- Refers to molecules that are structurally identical except for differences in the 3-dimensional configuration.

Endemic -- Something that is always present in a population but not always prevalent or present in high numbers. Often applied to diseases or infestations.

Endospore -- A thick-walled body containing genetic material that forms inside the vegetative cell of some types of bacteria, including Bacillus, under adverse conditions. When conditions improve, the endospore can develop into a vegetative cell.

Enzymes -- A biological catalyst; a protein, produced by an organism itself, that enables the splitting (as in digestion) or fusion of other chemicals.

Epidemiology Study -- A study of a human population or human populations.

Epidermis -- The outermost layer of the skin.

Erythema -- A name applied to redness of the skin produced by congestion of the capillaries, which may result from a variety of causes.

Erythrocyte -- Red blood cell.

Exposure assessment -- The process of estimating the extent to which a population will come into contact with a chemical or biological agent.

Extra Risk -- The risk in the population that can be attributed to exposure to the agent.

Extrapolation -- The use of a model to make estimates outside of the observable range.

Fibroma -- A benign tumor composed mainly of fibrous or fully developed connective tissue.

Fibrosarcoma -- A malignant tumor derived from fibroblasts that produce collagen.

Foray -- One of the commercial formulations of **B.t.k.** See Table 4-1.

Formulation -- A commercial preparation of a chemical including any inerts or contaminants.

Frank effects -- Obvious signs of toxicity.

Frank-effect Level (FEL) -- The dose or concentration of a chemical or biological agent that causes gross and immediately observable signs of toxicity.

Frass -- Larval excrement

Gavage -- The placement of a toxic agent directly into the stomach of an animal, using a gastric tube.

Genotoxic -- Causing direct damage to genetic material. Associated with carcinogenicity.

Geometric Mean -- The measure of an average value often applied to numbers for which a log normal distribution is assumed.

Gestation -- The period between conception and birth; in humans, the period known as pregnancy.

Haber's Law -- In toxicology, the assumption that the concentration or dose times (multiplied by) the duration of exposure (time) will always have the same effect. This relationship is true for some chemicals and some endpoints but not true for others. Even when true for a particular chemical and effect, it may be true only over certain ranges of exposure.

Half-time or Half-life -- For compounds that are eliminated by first-order kinetics, the time required for the concentration of the chemical to decrease by one-half.

Hazard Quotient (HQ) -- The ratio of the estimated level of exposure to the RRV or some other index of acceptable exposure.

Hazard identification -- The process of identifying the array of potential effects that an agent may induce in an exposed human population.

Heinz Bodies -- Dark-staining granules found in red blood cells, which are signs of oxidative damage. The formation of Heinz bodies can lead to red cell dysfunction and breakdown of the cell membrane.

Hemangiosarcoma -- A malignant tumor formed by proliferation of endothelial and fibroblastic tissue.

Hematological -- Pertaining to the blood.

Hematology -- One or more measurements regarding the state or quality of the blood.

Histamine -- A naturally occurring chemical that causes dilation of the capillaries and muscle contraction.

Histopathology -- Signs of tissue damage that can be observed only by microscopic examination.

Humoral -- Associated with agents dissolved in the blood or body fluids, in contrast to materials contained in cells (cell-mediated).

Hydroxylation -- The addition of a hydrogen-oxygen or hydroxy (-OH) group to one of the rings. Hydroxylation increases the water solubility of aromatic compounds. Particularly when followed by conjugation with other water soluble compounds in the body, such as sugars or amino acids, hydroxylation greatly facilitates the elimination of the compound in the urine or bile.

Hypoactivity -- Less active than normal.

Immunocompetent -- An organism with normal immune function.

Immunocompromised -- An organism with impaired immune function. Implies that the organism originally had normal immune function and that the impairment was caused by an external stress such as a chemical or disease.

Immunodeficient -- An organism with impaired immune function.

In vivo -- Occurring in the living organism.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

Inerts -- Adjuvants or additives in commercial formulations of gypsy moth control agents that do not cause mortality in the gypsy moth.

Intercept -- In a simple linear equation, the value of the dependent variable when the independent variable is zero.

Interpolation -- The use of mathematical models within the range of observations

Intraperitoneal -- Injection into the abdominal cavity.

Invertebrate -- An animal that does not have a spine (backbone).

Iritis -- Inflammation of the iris.

Irritant Effect -- A reversible effect, compared with a corrosive effect.

Larva (pl. larvae) -- An insect in the earliest stage after hatching. The larvae of gypsy moths are commonly called caterpillars.

Lepidopteran -- Pertaining to butterflies or moths.

Lethal Concentration$_{50}$ (LC_{50}) -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{50}$ (LD_{50}) -- The dose of a chemical calculated to cause death in 50% of a defined experimental animal population.

Lethargy -- A decrease in the normal amount of activity.

Lipophilic -- Having a tendency to dissolve or partition to fatty substances.

Lowest-Observed-Adverse-Effect Level (LOAEL) -- The lowest dose of a chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Malignant -- Cancerous.

Mammary gland -- The breast.

Metabolite -- A compound formed as a result of the metabolism or biochemical change of another compound.

Metastatic -- Pertaining to or of the nature of metastasis--the transfer of disease from one organ or part to another not directly connected with it. It may be due either to the transfer of pathogenic microorganisms (e.g., bacilli) or to the transfer of cells, as in malignant tumors.

Methemoglobin -- The chemical oxidation of the heme iron in hemoglobin from the ferrous (Hb^{++}) to the ferric state ($MetHb^{+++}$), resulting in the inability of hemoglobin to combine reversibly with oxygen.

Microorganisms -- A generic term for all organisms consisting only of a single cell, such as bacteria, viruses, and fungi.

Microsomal -- Pertaining to portions of cell preparations commonly associated with the oxidative metabolism of chemicals.

Minimal Risk Level (MRL) -- A route-specific (oral or inhalation) and duration- specific estimate of an exposure level that is not likely to be associated with adverse effects in the general population, including sensitive subgroups.

Mixture of Concern -- The mixture on which a risk assessment is being conducted. In the U.S. EPA Guidelines for the Risk Assessment of Complex Mixtures (U.S. EPA 1986a), the term, mixture of concern, is used in contrast to the term, similiar mixtures. See **Sufficient similarity** below.

Most Sensitive Effect -- The adverse effect observed at the lowest dose level, given the available data. This is an important concept in risk assessment because, by definition, if the most sensitive effect is prevented, no other effects will develop. Thus, RRVs and other similar values (Table 2-3) are normally based on doses at which the most sensitive effect is not likely to develop.

Multiple Chemical Sensitivity -- A syndrome that affects individuals who are extremely sensitive to chemicals at extremely low levels of exposure.

Mutagenicity -- The ability to cause genetic damage (that is damage to DNA or RNA). A mutagen is substance that causes mutations. A mutation is change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

NADH -- A molecule that is common in all living systems and is necessary for the proper function of many enzymes.

Necropsy -- Examination of a body after death. Usually refers to a gross examination of the major organs.

Neuropathy -- Damage to the peripheral nervous system.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of a chemical at which no statistically or biologically significant increases in frequency or severity of adverse effects were observed between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

No-Observed-Effect Level (NOEL) -- The dose of a chemical at no treatment-related effects were observed.

Normal Distribution -- One of several standard patterns used in statistics to describe the way in which variability occurs in a populations.

Occlusion Bodies -- Virus particles containing variable numbers of genetic material within one protein envelope.

Octanol-Water Partition Coefficient (K_{ow}) -- The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

Ocular -- Pertaining to the eye.

Ophthalmic -- Pertaining to the eye, as an ophthalmic solution--a solution of medication intended to be applied to the eye.

Organoleptic -- Relating to an objectionable taste or smell.

Organophosphate -- A class of insecticides that are neurotoxic.

Osteosarcoma -- A malignant tumor derived from bone tissue.

Parenteral -- Any form of injection.

Partition -- In chemistry, the process by which a compound or mixture moves between two or more media.

Pathogens -- Any disease-producing microorangism.

Pathway -- In metabolism, a sequence of metabolic reactions.

Peroxide -- A molecule that contains two or more oxygen atoms in series, such as —O—O—. These molecules are often involved in the degradation of polymers, including proteins.

pH -- The negative log of the hydrogen ion concentration. A high pH (>7) is alkaline or basic and a low pH (<7) is acidic.

Pharmacokinetics -- The quantitative study of metabolism (i.e., the processes of absorption, distribution, biotransformation, elimination).

Pheromone -- A scent used to attract, seduce, or repel mates. In general, any chemical that stimulates a behavioral response in another individual. In the gypsy moth program, pheromone formulations such as Disparlure are used to attract male gypsy moths so that the population can be monitored.

Piloerection -- A condition in which the hair stands on end.

Plasma Cholinesterase -- Another term for **Pseudocholinesterase**. The normal physiological role of this cholinesterase is not known. Inhibition of this enzyme is considered an index of exposure to many organophosphate insecticides.

Plasma -- The fluid portion of the blood in which particulates are suspended.

Plasmid -- Subcellular elements in bacteria that contain genetic material for relatively narrow and specific traits. Plasmids can be transferred from one microorganism to another of the same species. Plasmid transfer may also occur between two microorganisms of different species.

Polymer -- A generic term for a molecule composed of repeating units of less complex molecules. For example, proteins are polymers of amino acids.

Polyvinyl chloride -- A nontoxic polymer of vinyl chloride.

Probit -- Measures of the standard deviation from the mean or 50% response level.

Proteinaceous -- Consisting or composed of proteins.

Proteolytic enzymes -- Enzymes that breakdown proteins. Enzymes such as these are involved in the conversion of prototoxins to toxins.

Prototoxins -- Proteins that can be converted to toxins.

Pruritis -- Itching; an unpleasant skin sensation that provokes the desire to rub or scratch.

Pseudocholinesterase -- A term for cholinesterase found in the plasma. The normal physiological role of this cholinesterase is not known. Inhibition of this enzyme is considered an index of exposure to many organophosphate insecticides.

Racemic Mixture -- A 50:50 blend of a (+)enantiomer and (-)enantiomer.

Reference Concentration -- Concentration in air (mg/m^3) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.

Reference Dose -- Oral dose (mg/kg/day) not likely to be associated with adverse effects over lifetime exposure, in the general population, including sensitive subgroups.

Renal -- Pertaining to the kidneys.

Reproductive Effects -- Adverse effects on the reproductive system that may result from exposure to a chemical or biological agent. The toxicity of the agents may be directed to the reproductive organs or the related endocrine system. The manifestations of these effects may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions dependent on the integrity of this system.

Rhinitis -- Inflammation of the mucous membranes of the nose.

Route of Exposure -- The way in which a chemical or biological agent enters the body. Most typical routes include oral (eating or drinking), dermal (contact of the agent with the skin), and inhalation.

Risk Reference Value (RRV) -- A generic term used in this risk assessment as an estimate of dose that is not likely to induce adverse health effects in humans under specific conditions of exposure such as duration and route.

Sarcoma -- A tumor made up of a substance like the embryonic connective tissue. Sarcomas are often highly malignant.

Scientific Notation -- The method of expressing quantities as the product of number between 1 and 10 multiplied by 10 raised to some power. For example, in scientific notation, 1 kg = 1,000 g would be expressed as 1 kg = 1×10^3 g and 1 mg = 0.001 would be expressed as 1 mg = 1×10^{-3}.

Scission -- In metabolism, breaking or cleavage of part of a molecule.

Septicemia -- The occurrence of pathogens or pathogenic toxins in the blood or other body fluids.

Serotype -- A classification of a microorganism based on occurrence of antigens in the cell.

Seta (pl. setae) -- Any tiny socketed projection from the exoskeleton (the hard case forming the outer surface of the body and appendages of an insect,) commonly hairlike in appearance.

Species to Species Extrapolation -- A method involving the use of exposure data on one species (usually an experimental mammal) to estimate the effects of exposure in another species (usually humans).

Squamous cell papillomas -- A type of benign tumor.

Standard Deviation -- An expression of the variability in a sample or population.

Standard Normal Distribution -- A normal distribution with a mean of 0 and a standard deviation of one.

Streptococcus (pl. streptococci) -- A genus of bacteria, which depending on its classification, may be associated with infections in humans.

Subchronic Reference Dose -- Oral dose (mg/kg/day) not likely to be associated with adverse effects over a less-than-lifetime exposure, in the general population, including sensitive subgroups.

Subchronic Exposure -- An exposure duration that can last for different periods of time, but 90 days is the most common test duration. The subchronic study is usually performed in two species (rat and dog) by the route of intended use or exposure.

Subconjunctival -- Refers to the area beneath the membrane that lines the eyelids and eyeball.

Subcutaneous -- An injection just below the skin.

Substrate -- With reference to enzymes, the chemical that the enzyme acts upon.

Succinylcholine -- A neuromuscular blocking agent.

Sufficient similarity -- As applied to chemical mixtures, whether or not the data on one or more samples of a complex and variable mixture can or should be used for dose-response assessments for all such mixtures.

Sulfhemoglobinemia -- The presence of abnormal pigments, other than methemoglobin, in red blood cells. A form of nonspecific oxidative damage to the blood.

Synapse -- The space between two nerve cells or a nerve cell and an effector cell such as muscle.

Synergistic Effect -- A situation is which the combined effects of two chemicals is much greater than the sum of the effect of each agent given alone.

Systemic Toxicity -- Effects that require absorption and distribution of a toxic agent to a site distant from its entry point at which point effects are produced. Systemic effects are the obverse of local effects.

Teratogenic -- Causing structural defects that affect the development of an organism; causing birth defects.

Teratology -- The study of malformations induced during development from conception to birth.

Threshold Limit Value (TLV) -- An air concentration (mg/m^3) not likely to cause adverse effects in exposed workers, over a normal period of working.

Threshold -- The maximum dose or concentration level of a chemical or biological agent that will not cause an effect in the organism.

Thuricide -- One of the commercial formulations of **B.t.k.** See Table 4-1.

Toxicity -- The inherent ability of an agent to affect living organisms adversely.

Toxins -- Chemicals that may cause toxic effects. Often used when referring to naturally occurring toxic agents, especially proteins.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RRV and similar values from experimental data. UFs are intended to account or (1) the variation in sensitivity among members of the human population; (2) the uncertainty in extrapolating animal data to the case of humans; (3) the uncertainty in extrapolating from data obtained in a study that is less than lifetime exposure; and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10. See table 2-4 for additional details.

Urinalysis -- Testing of urine samples to determine whether toxic or other physical effects have occurred in an organism.

Urticaria -- A skin condition marked by the development of wheals.

Vehicle -- A substance (usually a liquid) used as a medium for suspending or dissolving the active ingredient. Commonly used vehicles include water, acetone, and corn oil.

Vertebrate -- An animal that has a spinal column (backbone).

Volatile -- Referring to compounds or substances that have a tendency to vaporize. A material that will evaporate quickly.

Wheals -- A smooth, slightly elevated area on the body surface, which is redder or paler than the surrounding skin. It is often accompanied by severe itching and is usually changing in size or shape or disappearing within a few hours. It is the typical lesion of urticaria, the dermal evidence of allergy, and in sensitive persons may be provoked by mechanical irritation of the skin. Also called a hive.

Xenobiotic -- A chemical that does not naturally occur in an organism. Often applied generically to all synthetic or man-made chemicals.

Subject Index

This environmental impact statement mentions the use of insecticides. All uses of insecticides must be registered by appropriate State or Federal agencies, or both.

Some States have restrictions on the use of certain insecticides. Check State and local regulations. Also, because registrations of insecticides are under constant review by the U.S. Environmental Protection Agency, consult your county agricultural agent or State extension specialist to be sure the intended use is still registered.

Caution: Insecticides may injure humans, domestic animals, livestock, crops, beneficial insects, fish, and other wildlife if they are not handled or applied properly. Use all insecticides selectively and carefully. Follow the directions and heed all precautions on the labels.

Do not apply insecticides when there is danger of drift or in ways that may contaminate water or leave illegal residues.

Avoid prolonged inhalation of insecticide sprays or dusts; wear protective clothing and equipment if specified on the container.

If hands become contaminated with an insecticide, do not eat or drink until you have washed. In case an insecticide is swallowed or gets in the eyes, follow the first-aid treatment given on the label and get prompt medical attention. If an insecticide is spilled on your skin or clothing, remove clothing immediately and wash skin thoroughly.

Store insecticides in original containers out of the reach of children and animals, and away from food and feed.

Dispose of surplus insecticides and empty containers promptly, using recommended practices.

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